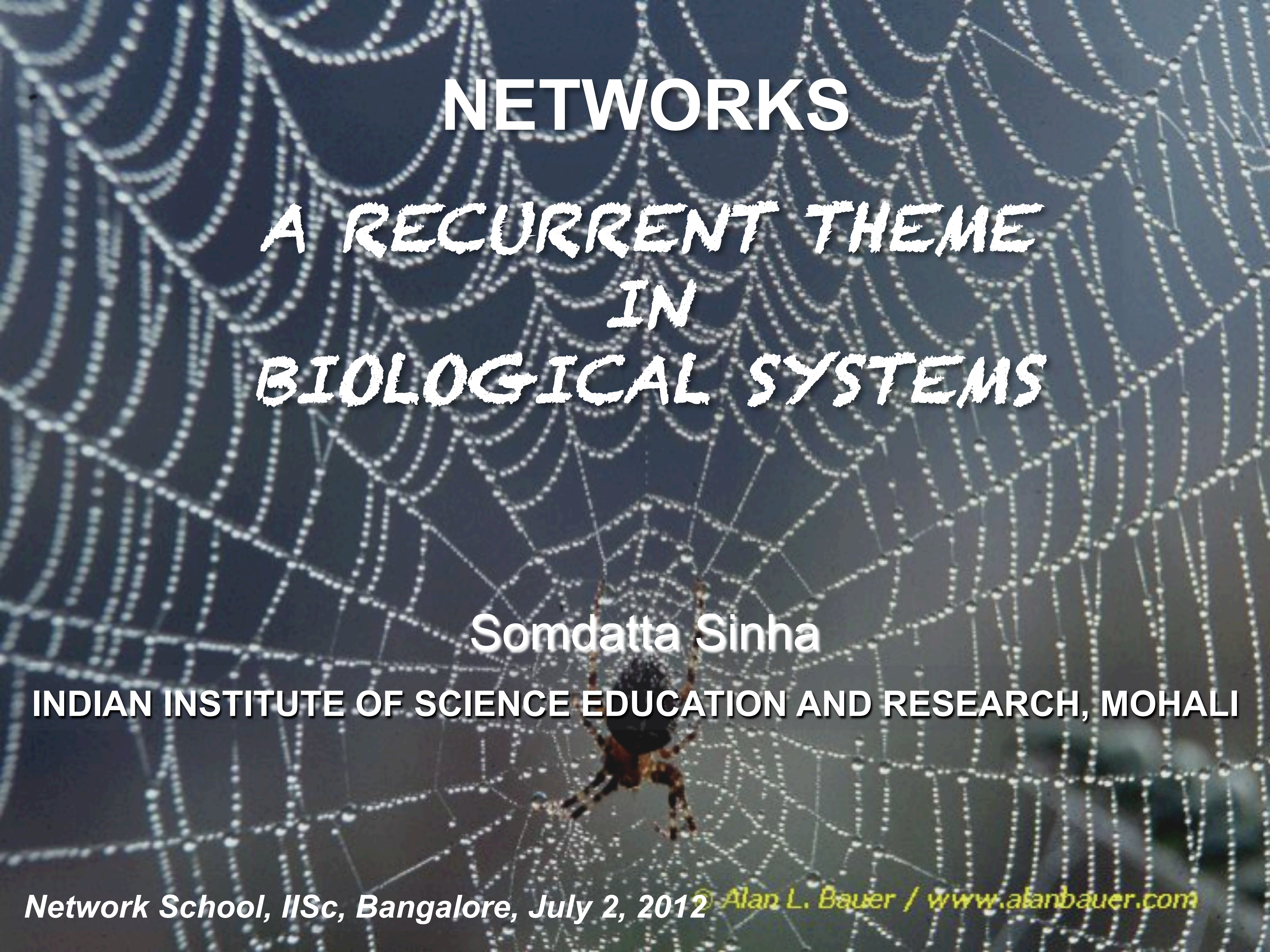

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NETWORKS

A RECURRENT THEME
IN
BIOLOGICAL SYSTEMS

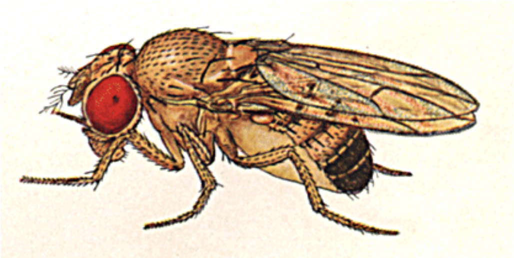
Somdatta Sinha

INDIAN INSTITUTE OF SCIENCE EDUCATION AND RESEARCH, MOHALI

Network School, IISc, Bangalore, July 2, 2012

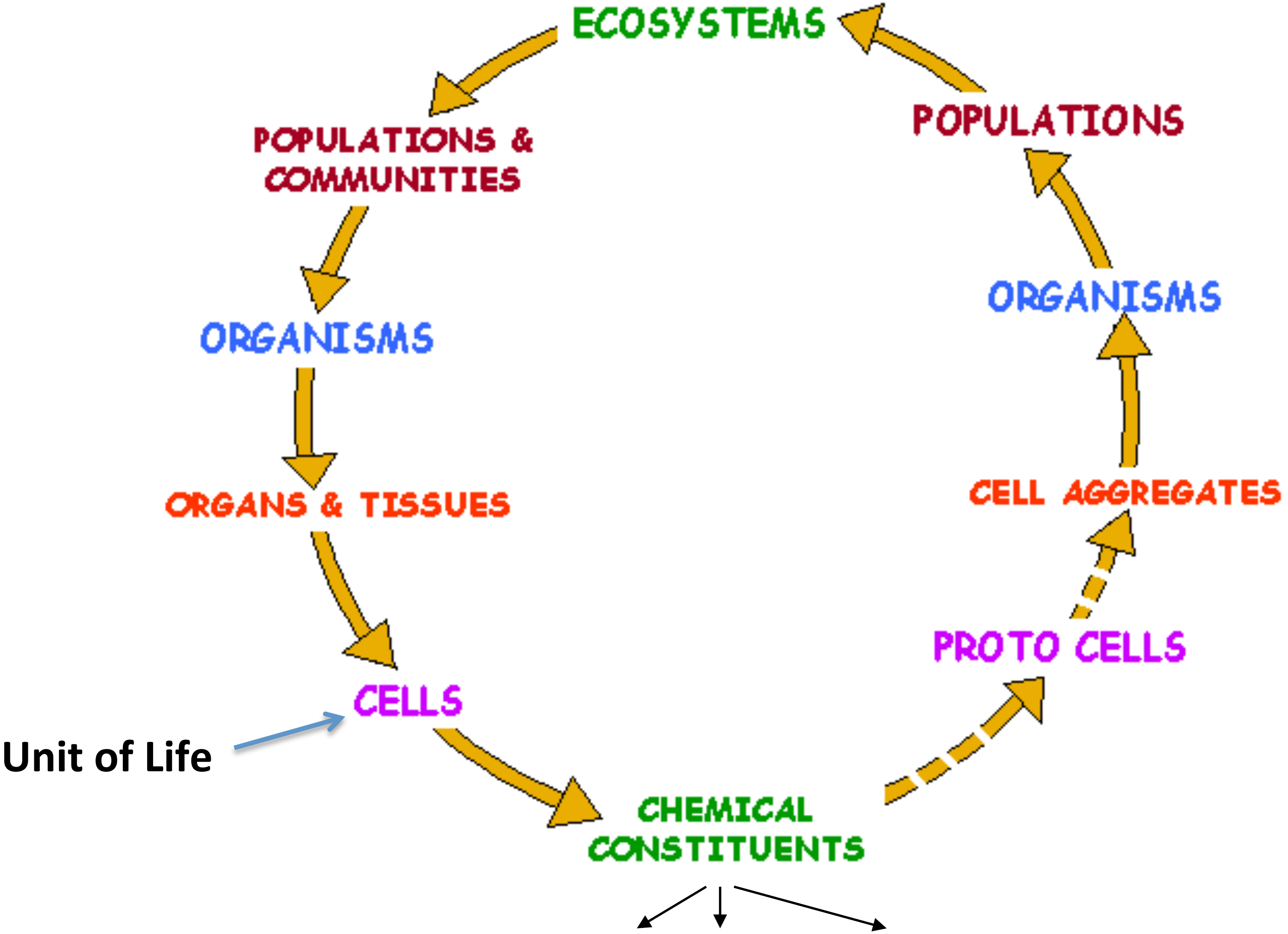







This is to acknowledge that several images and other material in this presentation are obtained from material available in the internet resources.

LEVELS OF ORGANISATION IN BIOLOGICAL SYSTEMS



ECOSYSTEMS

POPULATIONS & COMMUNITIES

ORGANISMS

ORGANS & TISSUES

CELLS

Unit of Life

CHEMICAL CONSTITUENTS

PROTO CELLS

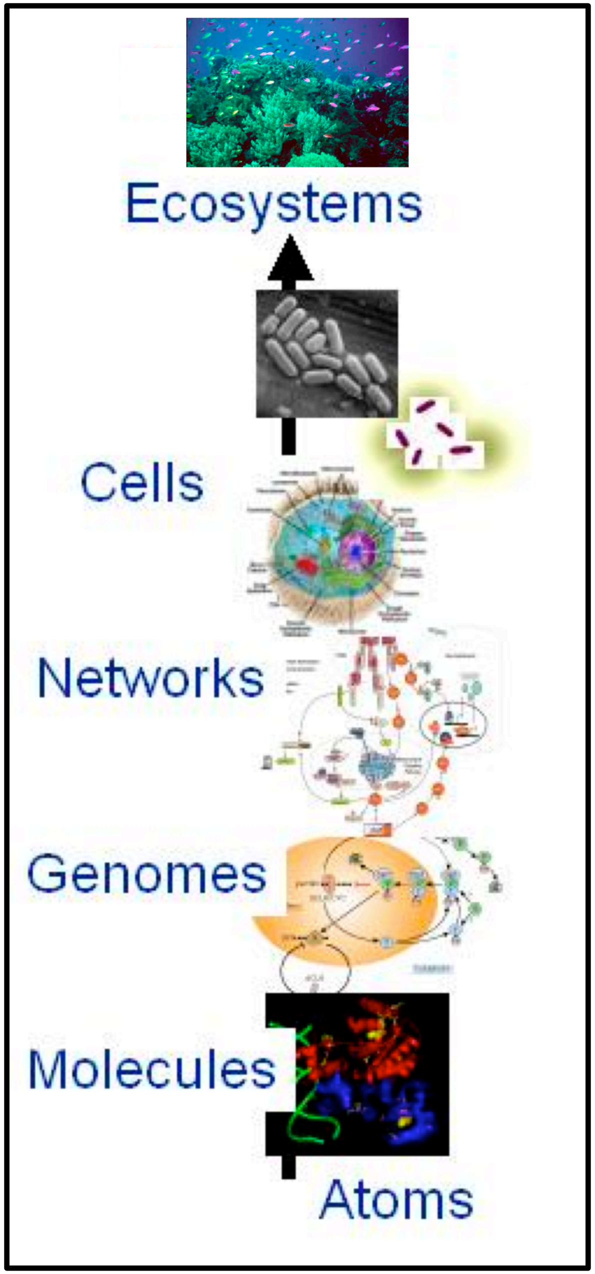
CELL AGGREGATES

ORGANISMS

POPULATIONS

DNA, RNA, Proteins, Lipid bilayer, mitochondria, etc

MULTISCALE DESCRIPTION



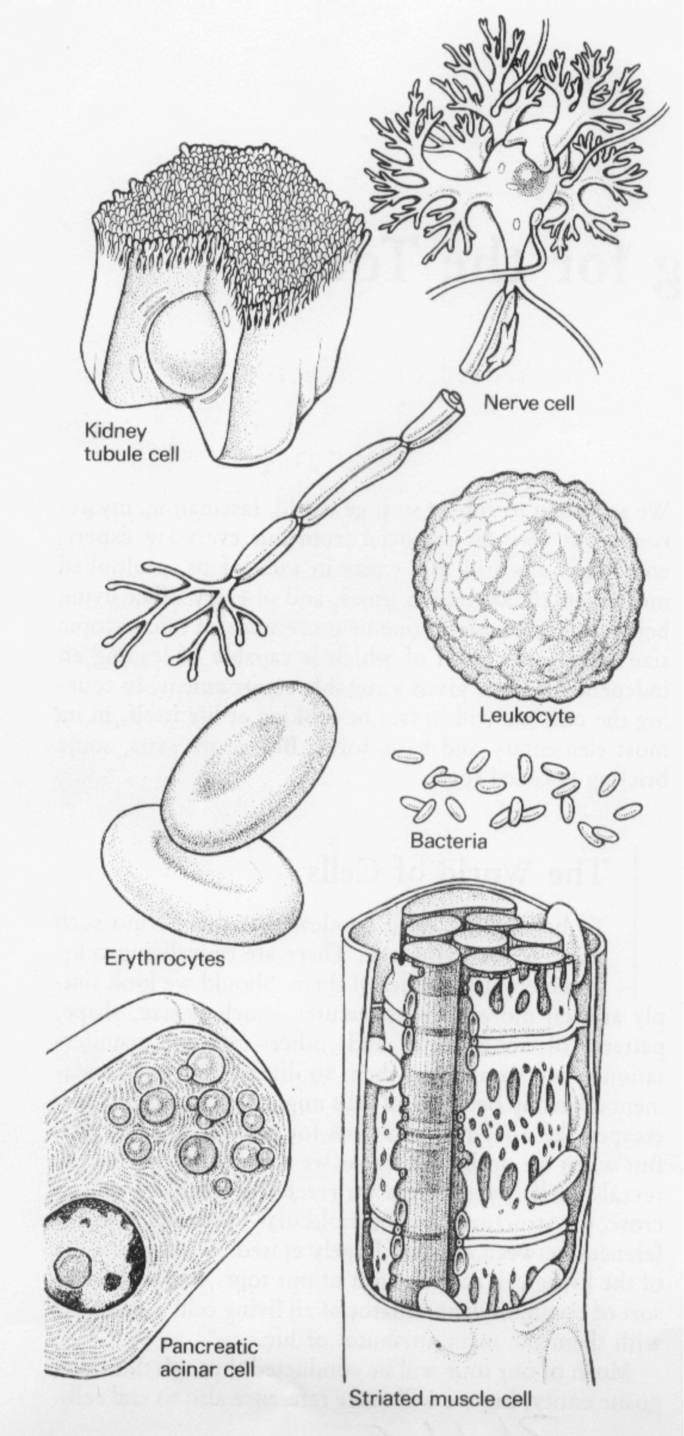
The challenge is

to connect different scales in both time and space

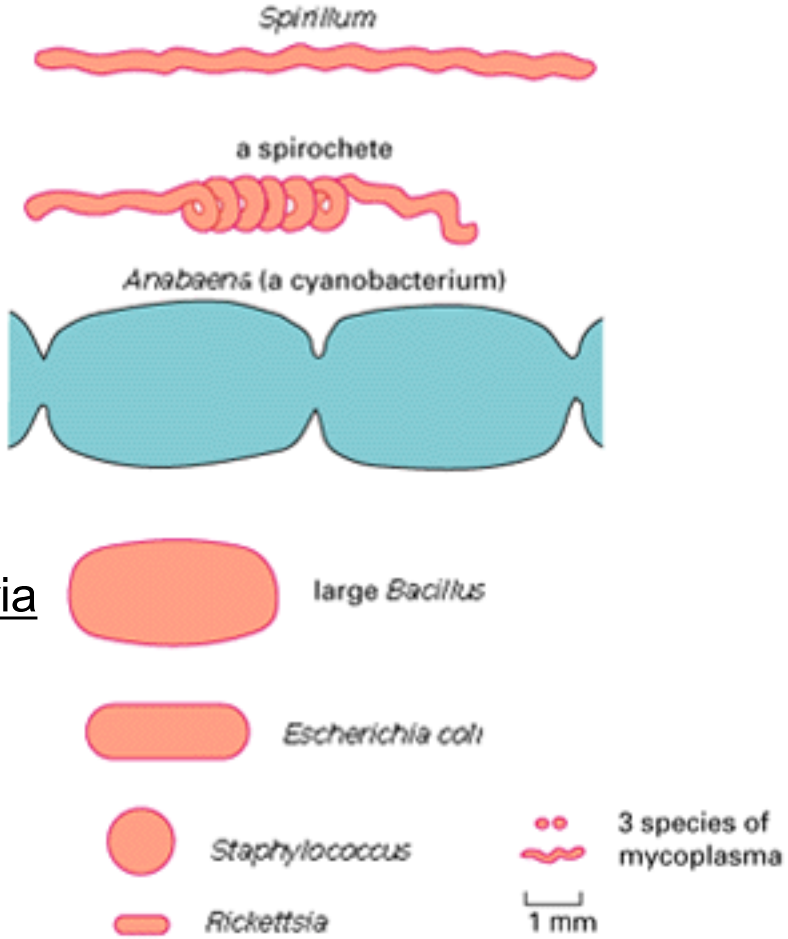
Information plus regulation

Organisation is limited by the communication between the subsystems

Living systems are made up of cells - *single or multi-cellular*

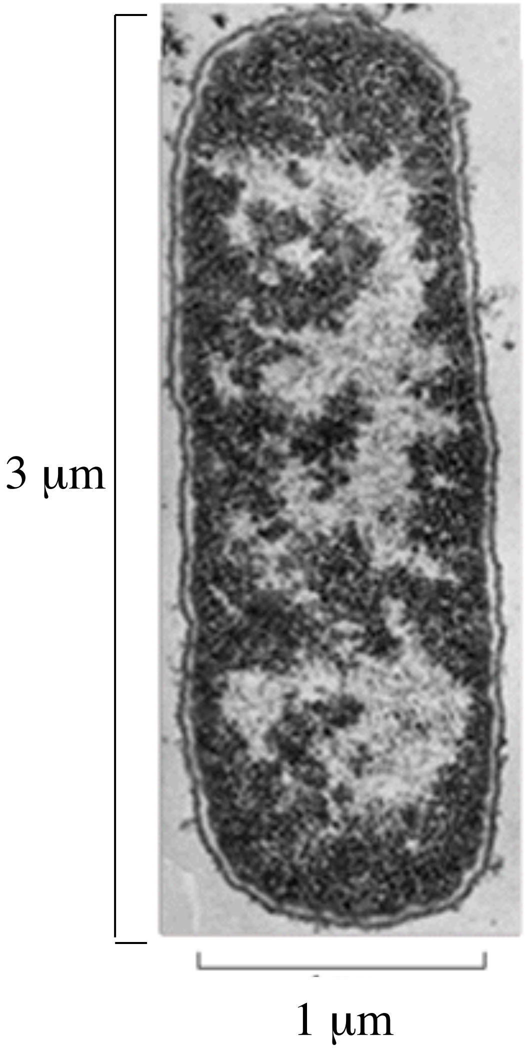


<u>Some bacteria</u>



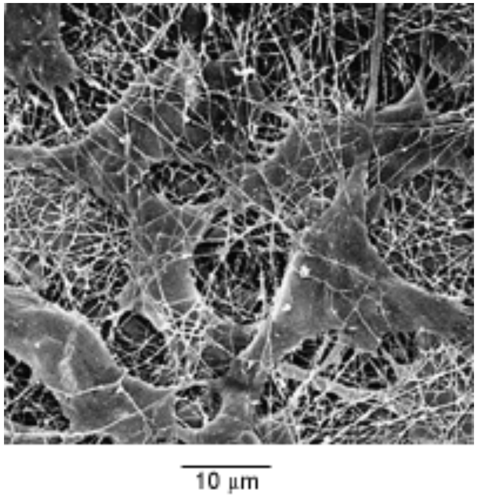
Smallest cell (mycoplasma) 0.0001 mm diameter

Large cells - nerve cells in giraffe’s neck -
~ 3 m (9.7 ft) in length.



Electron micrograph of E.coli.

Dividing E.coli.



Fibroblast cells in cornea of rat

(Scanning electron micrograph)

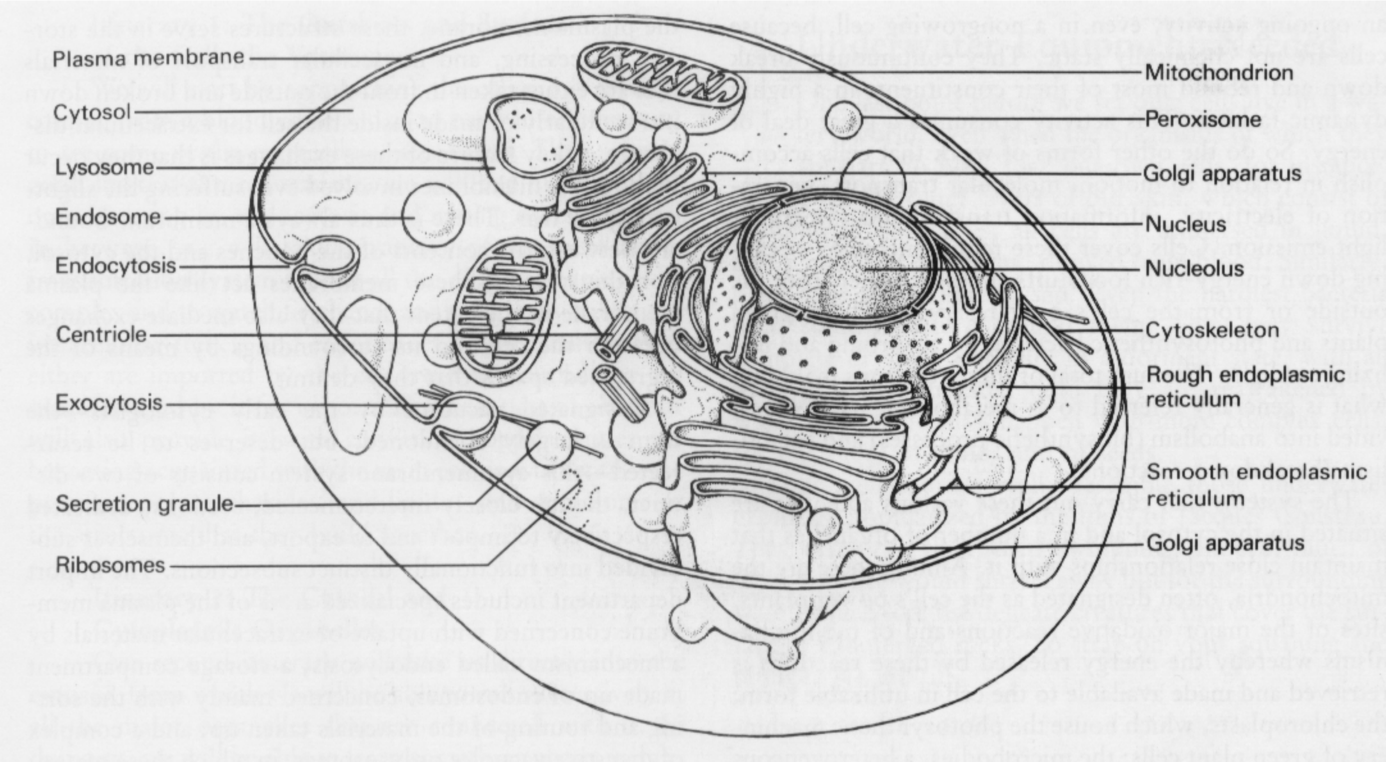
Collagen fibrils in ECM

Doubling time

The bacterium *E. coli* can reproduce in 20 minutes

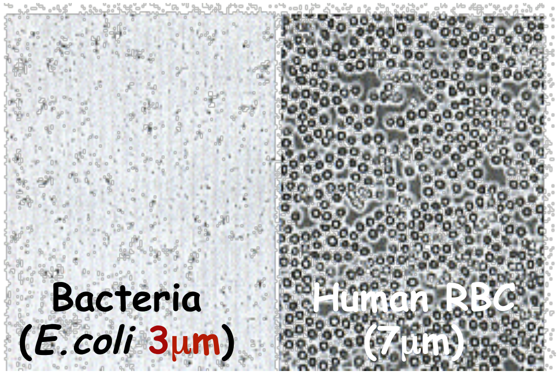
Cell cycle of single-celled yeast is 90 -120 minutes

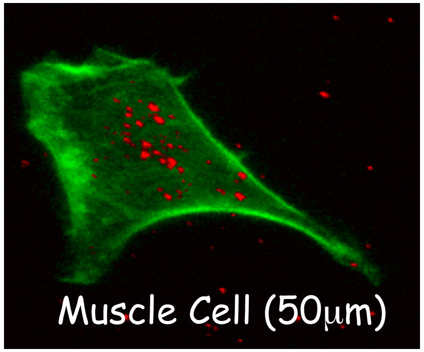
A rapidly dividing mammalian cell cycle is about 24 hours

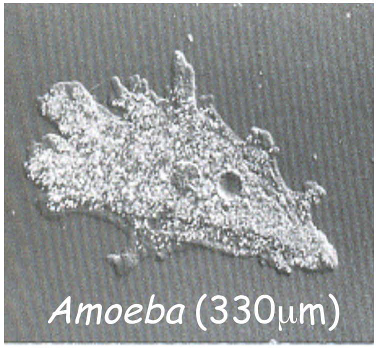


The Approximate Chemical Composition of a Bacterial Cell	Percent of Total Cell Weight	Types of Each Molecule
Water	70	1
Inorganic Ions	1	20
Sugars and precursors	1	250
Amino acids and precursors	0.4	100
Nucleotides and precursors	0.4	100
Fatty acids and precursors	1	50
Other small molecules	0.2	~300
Macromolecules (proteins, nucleic acids, and polysaccharides)	26	~3000

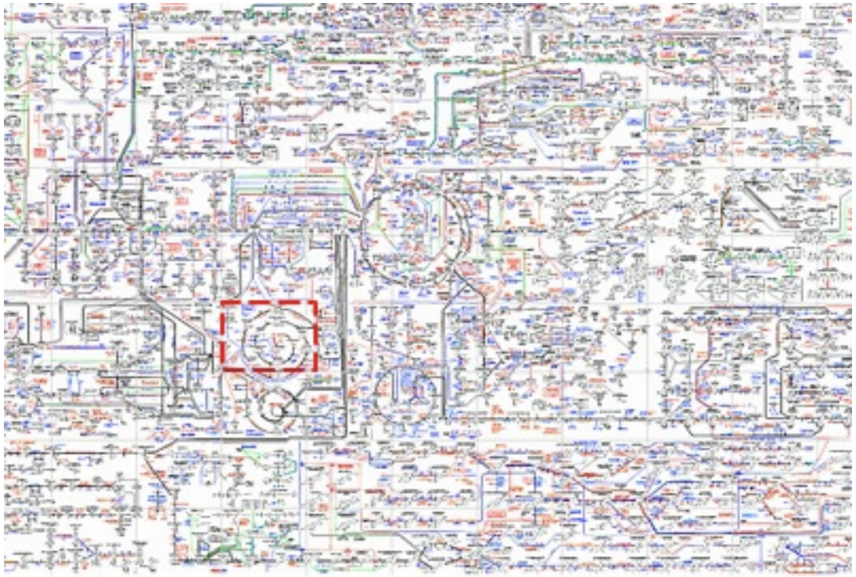
Some numbers







Cellular functions are controlled by networks of biochemical reactions



Cellular behaviour is an emergent property of networks of inter-connected multi-step chemical reactions of the molecular species in the cell.

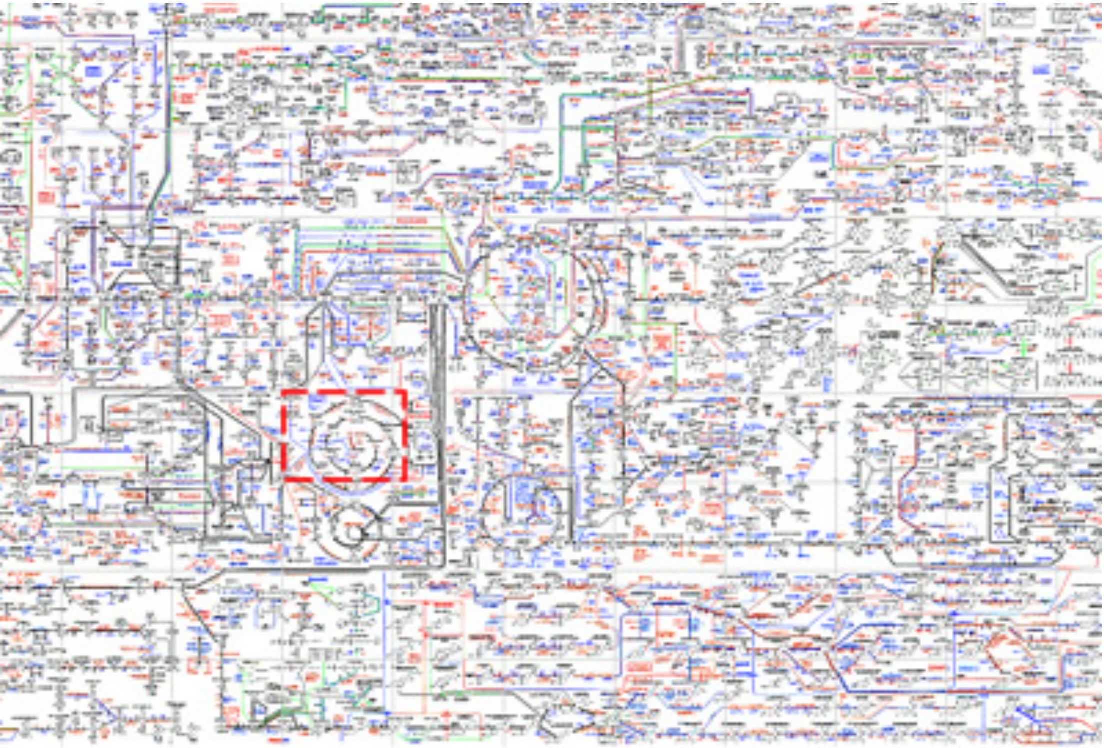
- ***Co-ordination***
- ***Regulation***
- ***Decision-making***
- ***Ability to evolve***

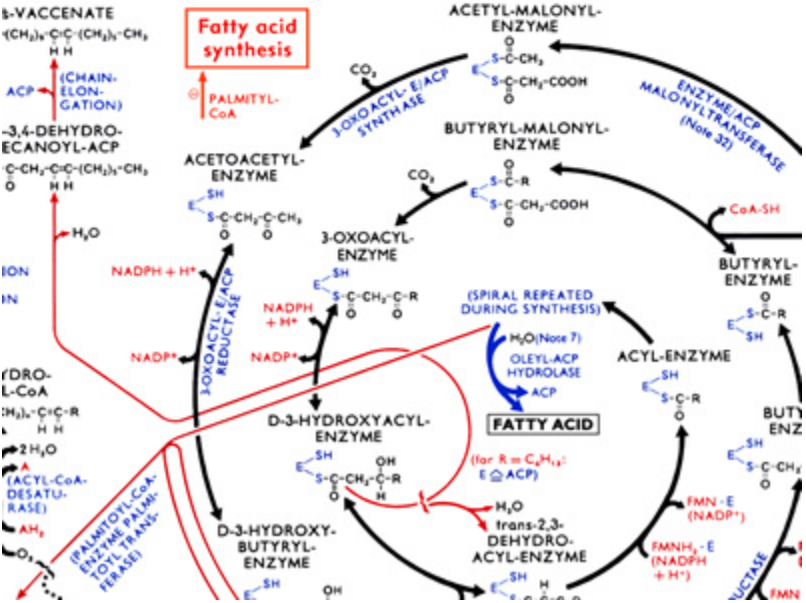
CHEMISTRY & PHYSICS DRIVE ALL LIFE PROCESSES

Cellular functions are controlled by multi-step biochemical reactions

These are inter-connected chemical reactions forming an intricate network of functional and physical interactions between molecular species in the cell.

- *Synthesis and breakdown of required biomolecules*,
- *Sensing and transduction of intra and extra-cellular signals*,
- *Facilitation of cross talk among different processes in different compartments in the cell.*





http://www.expasy.ch/cgi-bin/show_thumbnails.pl

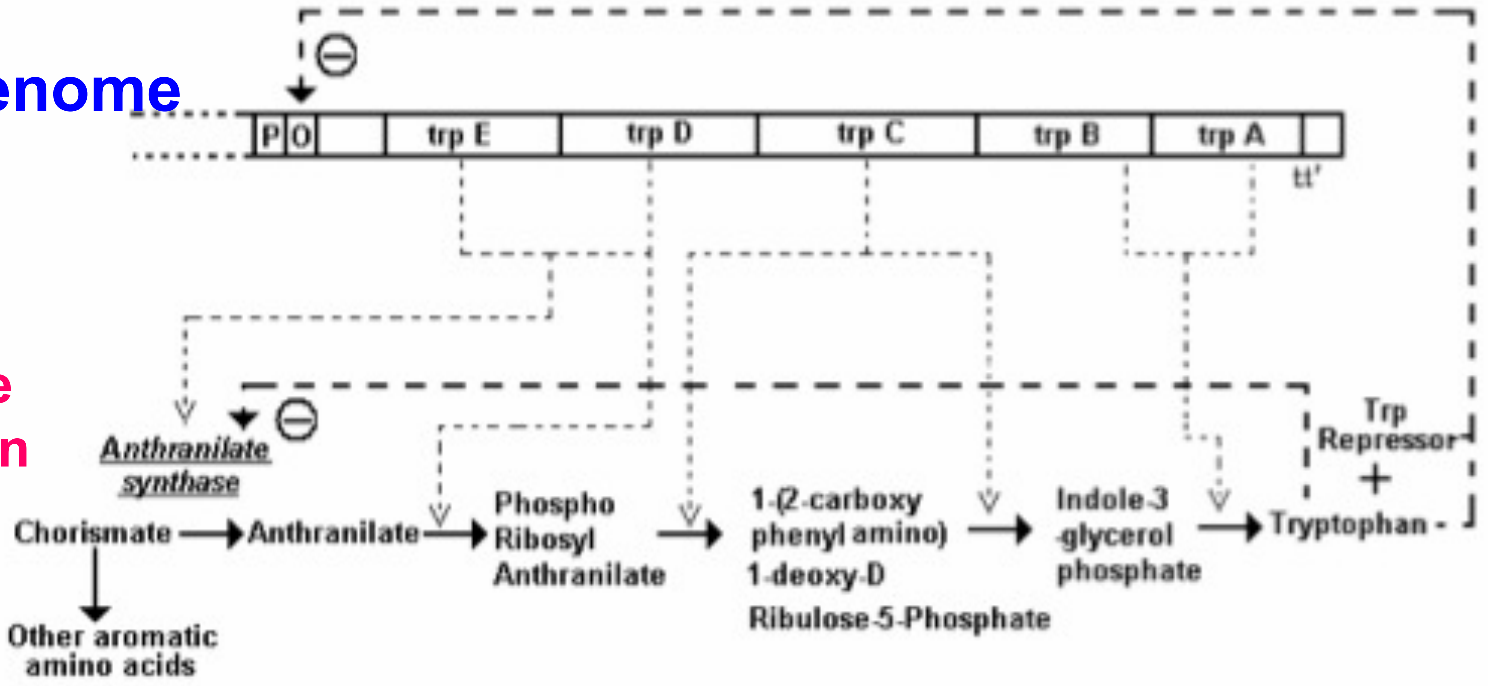
Complex network of biochemical reactions in cells co-ordinate and control cellular functions

TRYPTOPHAN BIOSYNTHETIC PATHWAY IN *E coli.*

Gene Repression

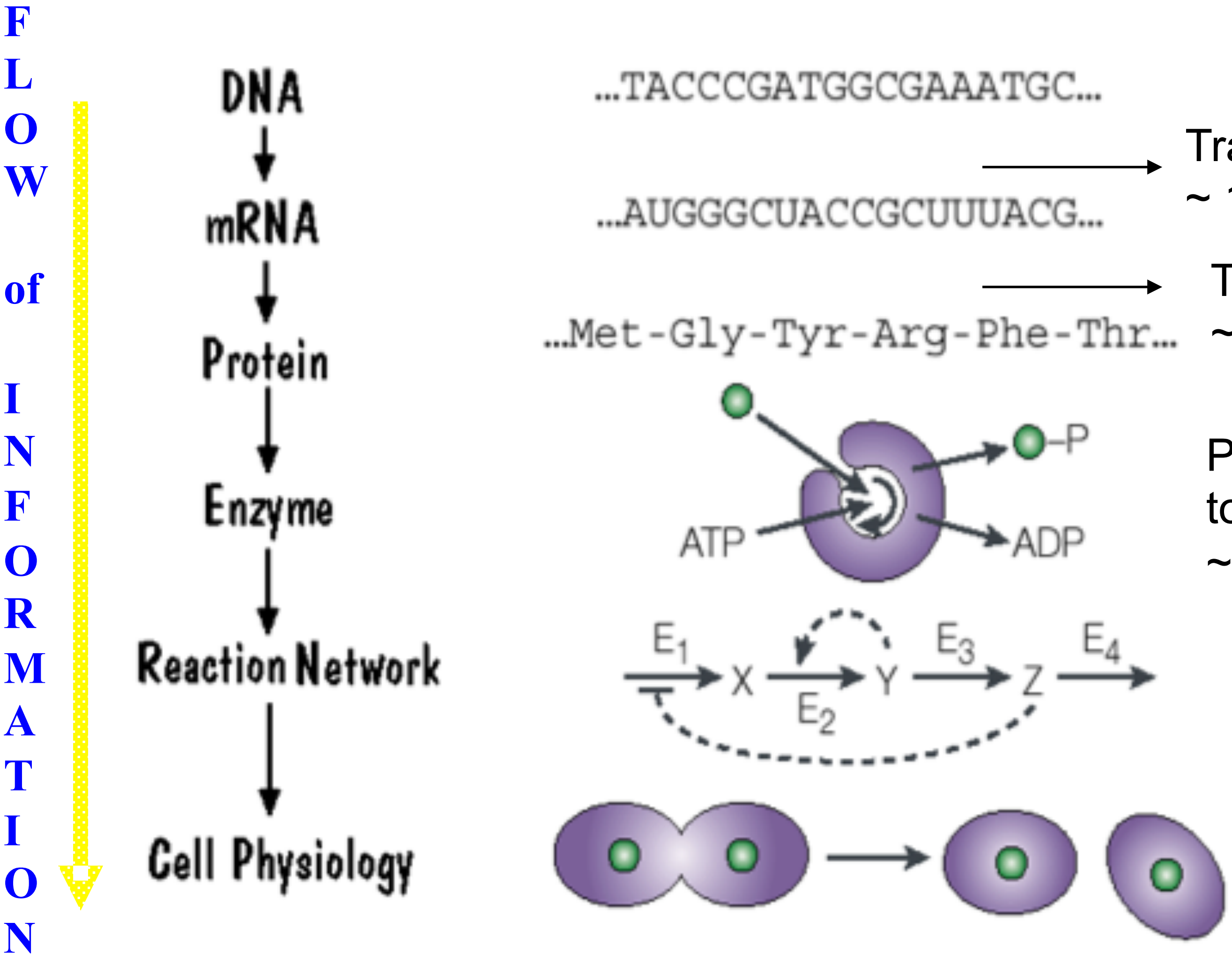
DNA/Genome

Enzyme inhibition



Genetic and Metabolic reactions and their regulation

The Central Dogma

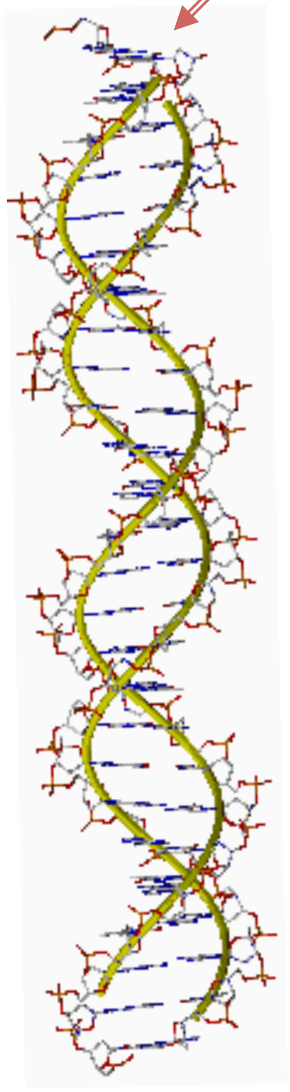


Transcription rate -
~ 1,000 nucleotides/minute

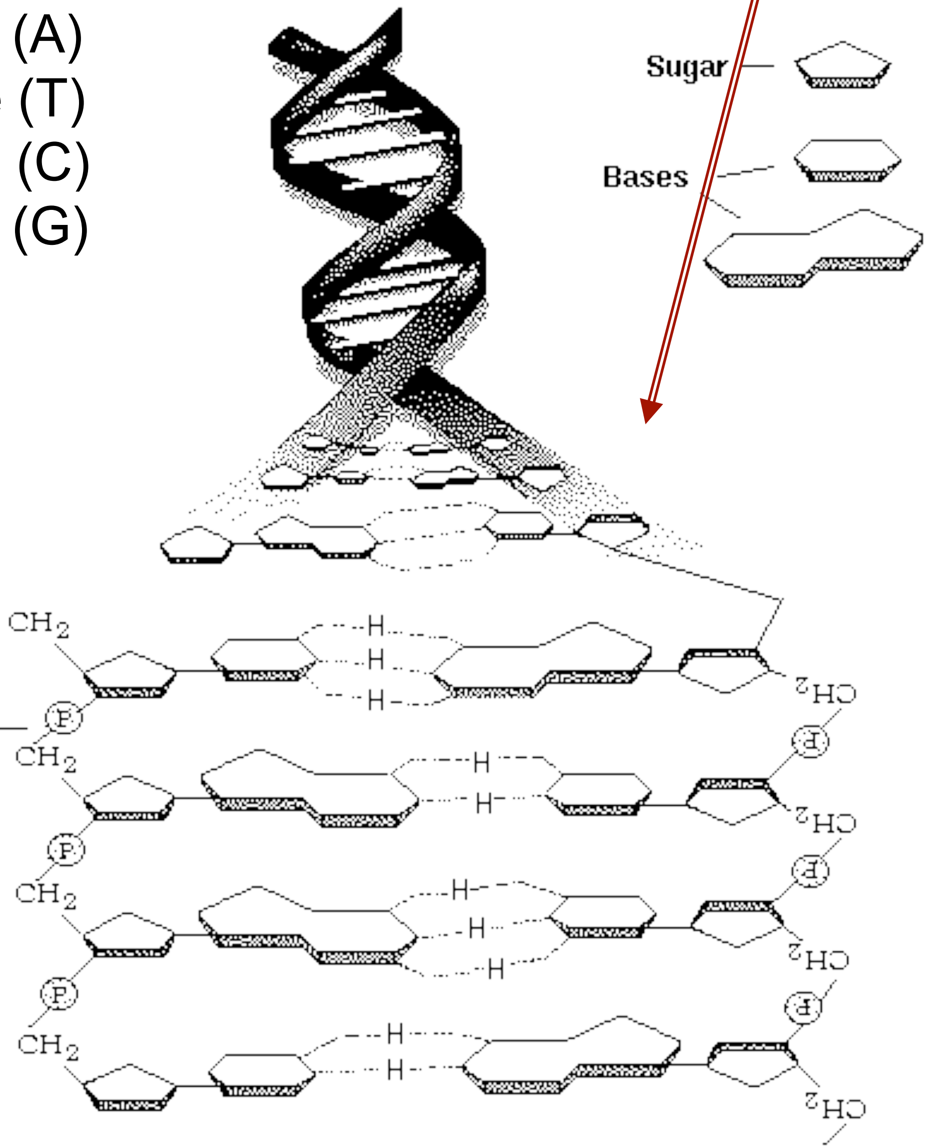
Translation rate -
~ 900 amino acids/minute

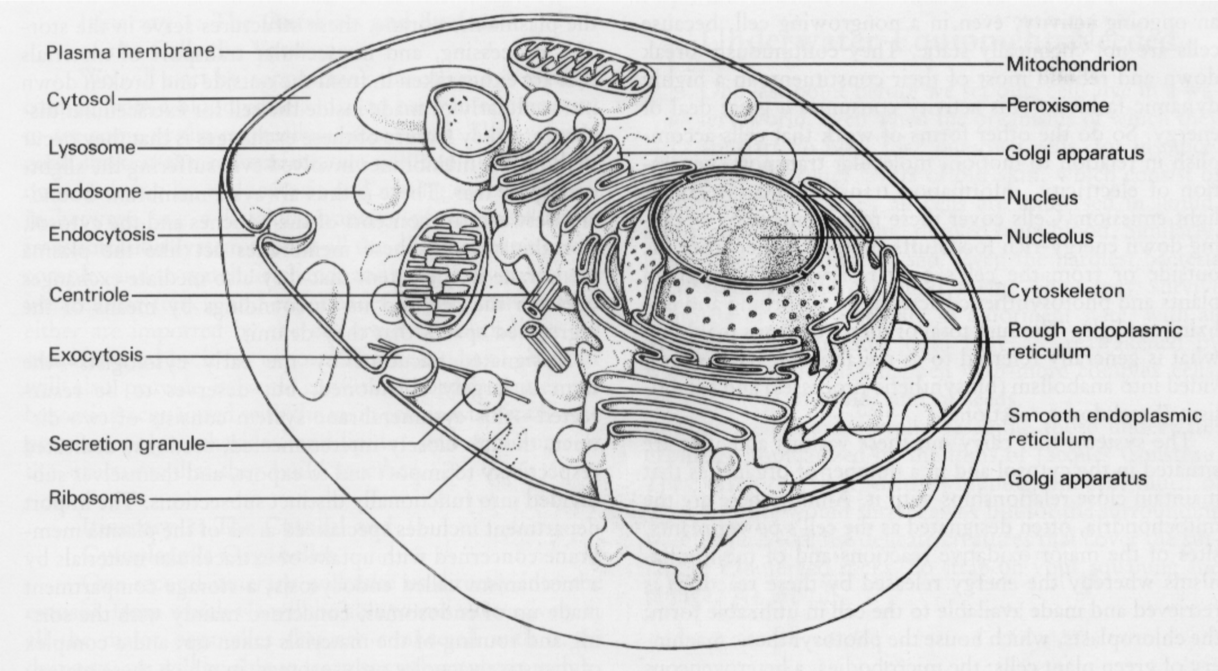
Production of the protein
to the binding of dimer –
~ 3 minutes

Double Helical Structure of DNA facilitates its replication



Adenine (A)
Thymine (T)
Cytosine (C)
Guanine (G)





E.coli genome is ~1.2 mm (4 million base pairs)
Human genome length is ~2 metre (3000 million bp)

A gene is a region of DNA whose final product is either a polypeptide or an RNA molecule

Smallest gene ~10000 base
Largest gene ~ 2 million bases

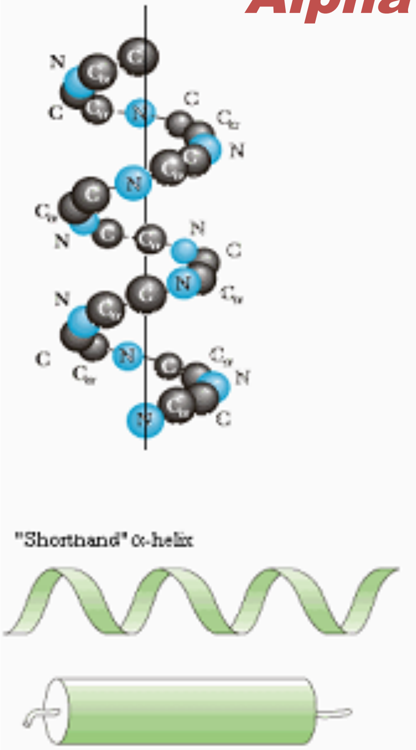
Ovalbumin (7.7Kbp)
a human muscle protein

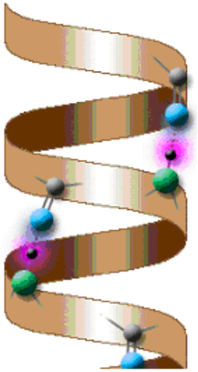
Transcription
(movie from Virtual Cell Animation Centre)

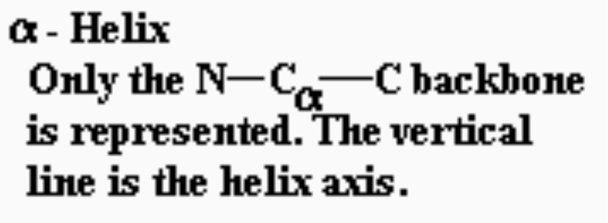
Translation
(movie from Virtual Cell Animation Centre)

Amino acid sequences in proteins form patterns of specific secondary structures useful for their function

Alpha Helix

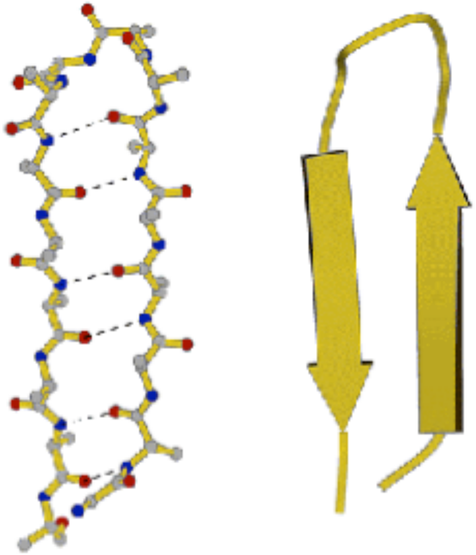






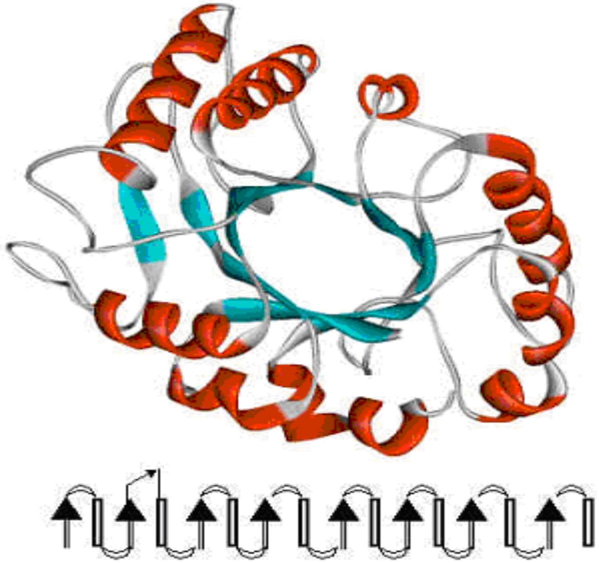
α - Helix
Only the N—C_α—C backbone is represented. The vertical line is the helix axis.

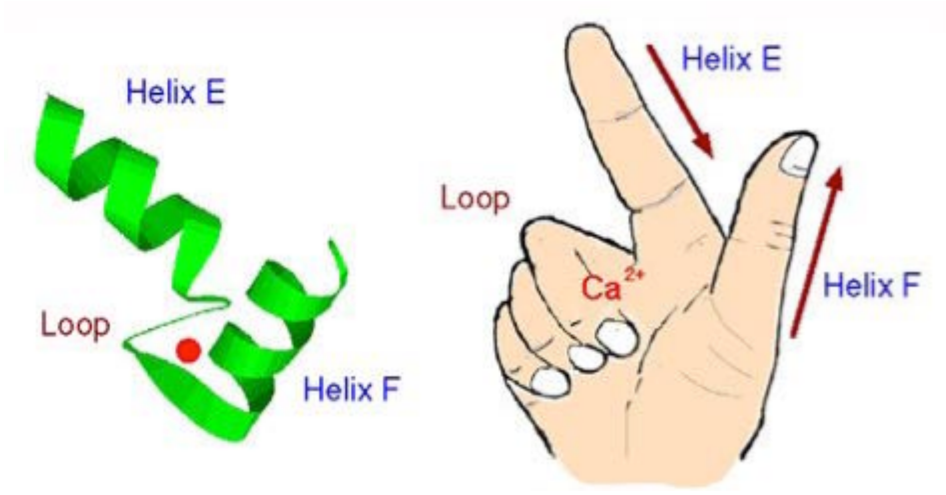
Beta sheet



Parallel chains

Combinations of secondary structural elements form different patterns of *Super Secondary Structures* (folds) that perform specific functions



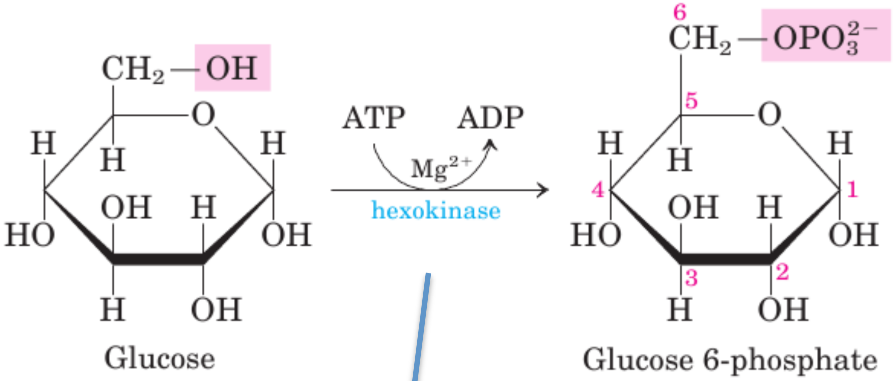


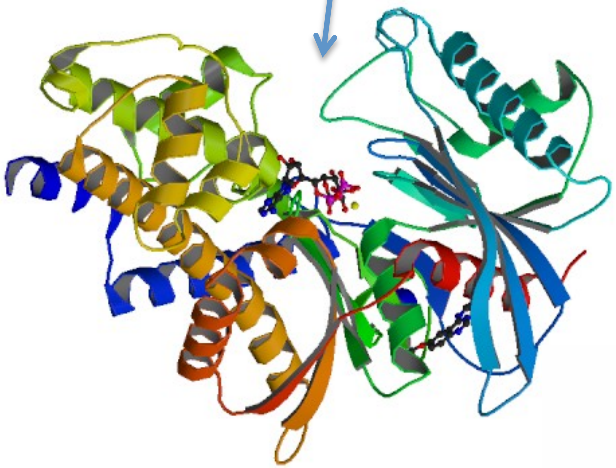
TIM Barrel

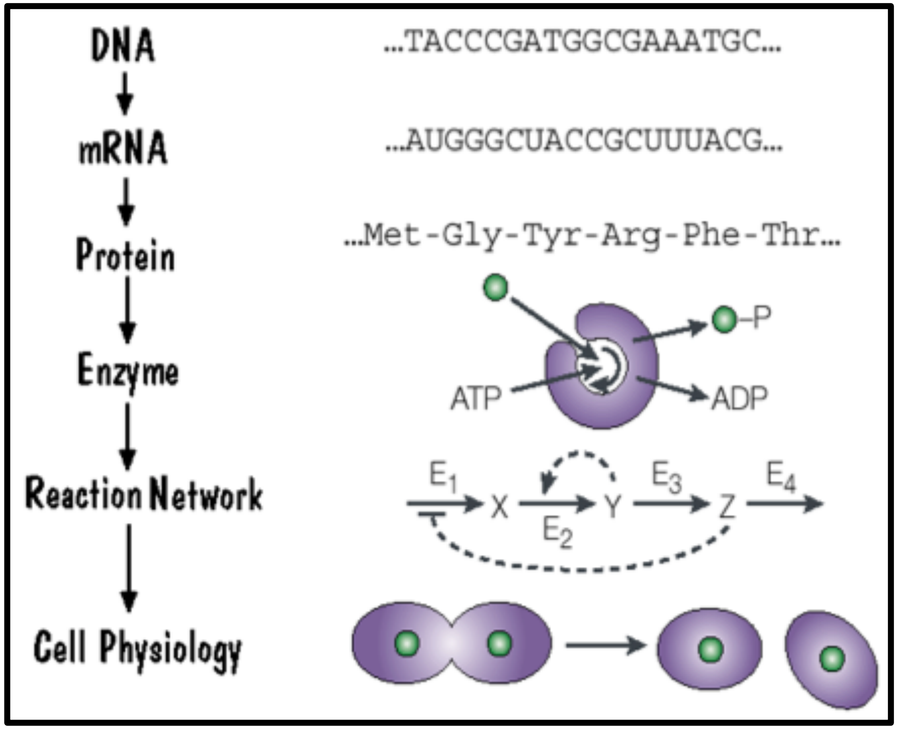
An eight-stranded α/β domain (*first found in Triose phosphate isomerase*). A central barrel formed by parallel β-strands surrounded by seven or eight α helices which shield the barrel from solvent.

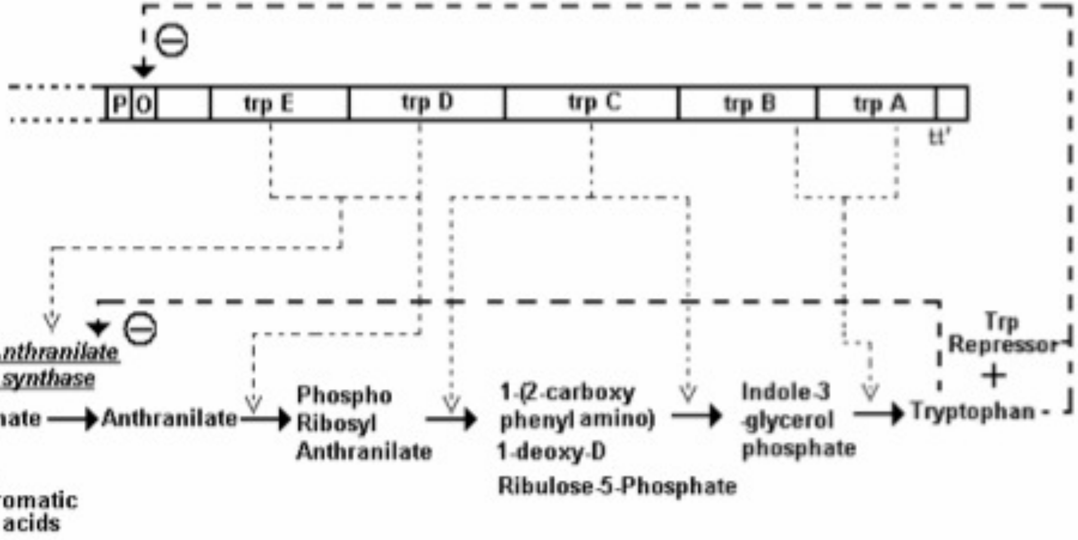
EF Hand

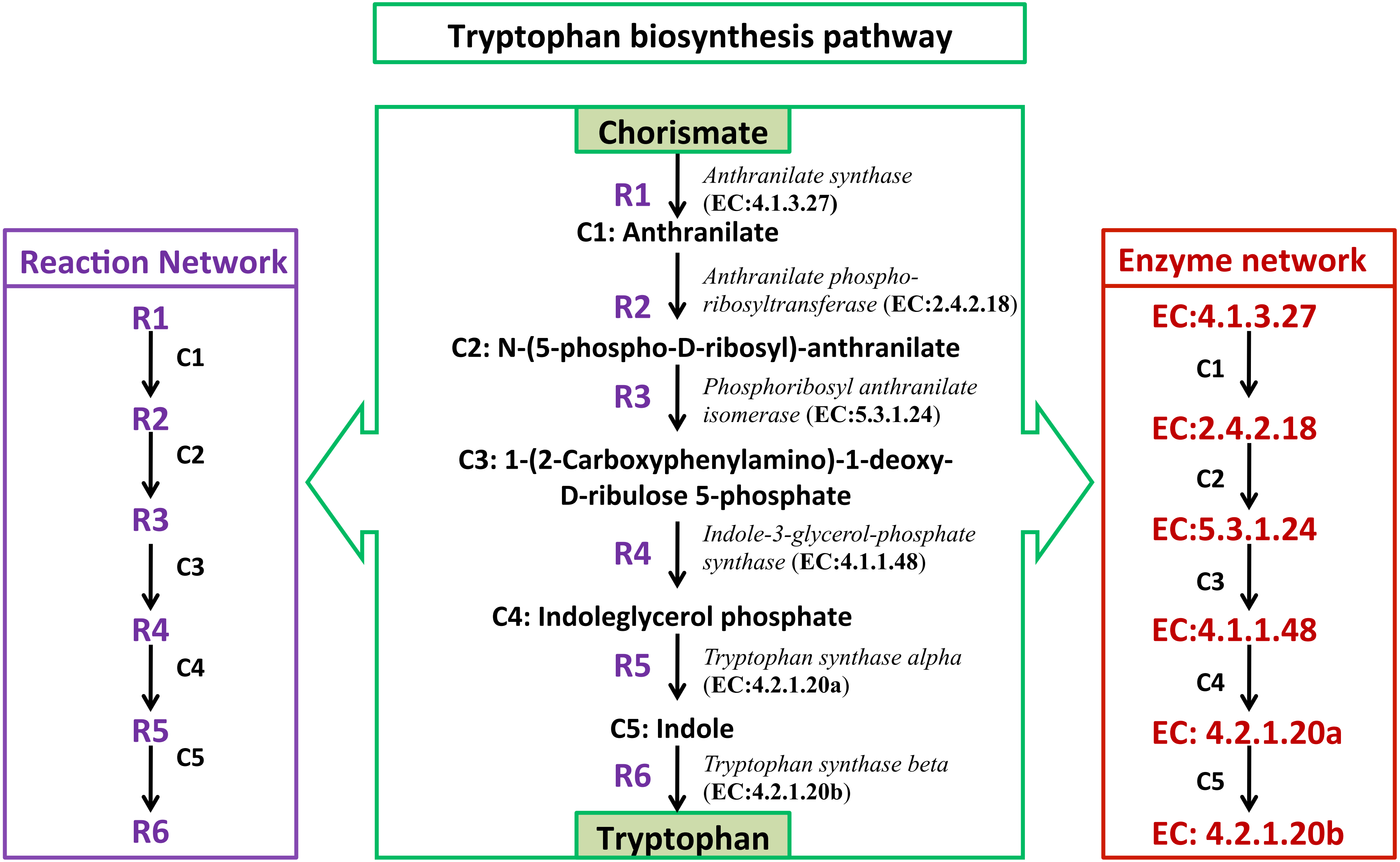
The loop region in Calcium binding proteins are enriched in Asp, Glu, Ser, and Thr.


CH2—OH
O
H
H
H
HO
OH
H
OH
H
OH
Glucose
ATP
ADP
Mg2+
hexokinase
6
CH2—OPO3 2−
5
O
H
H
H
4
HO
OH
H
1
OH
3
H
2
OH
Glucose 6-phosphate




DNA
...TACCCGATGGCGAAATGC...
mRNA
...AUGGGCUACCGCUUUACG...
Protein
...Met-Gly-Tyr-Arg-Phe-Thr...
Enzyme
P
ATP
ADP
Reaction Network
E1
X
E2
Y
E3
Z
E4
Cell Physiology


P
O
trp E
trp D
trp C
trp B
trp A
tt'
Anthranilate synthase
Trp Repressor
+
Chorismate
Anthranilate
Phospho Ribosyl Anthranilate
1-(2-carboxy phenyl amino) 1-deoxy-D Ribulose-5-Phosphate
Indole-3 -glycerol phosphate
Tryptophan
Other aromatic amino acids



Tryptophan biosynthesis pathway

Chorismate

R1 *Anthranilate synthase* (EC:4.1.3.27)

C1: Anthranilate

R2 *Anthranilate phosphoribosyltransferase* (EC:2.4.2.18)

C2: N-(5-phospho-D-ribosyl)-anthranilate

R3 *Phosphoribosyl anthranilate isomerase* (EC:5.3.1.24)

C3: 1-(2-Carboxyphenylamino)-1-deoxy-D-ribulose 5-phosphate

R4 *Indole-3-glycerol-phosphate synthase* (EC:4.1.1.48)

C4: Indoleglycerol phosphate

R5 *Tryptophan synthase alpha* (EC:4.2.1.20a)

C5: Indole

R6 *Tryptophan synthase beta* (EC:4.2.1.20b)

Tryptophan

Reaction Network

R1 → C1 → **R2** → C2 → **R3** → C3 → **R4** → C4 → **R5** → C5 → **R6**

Enzyme network

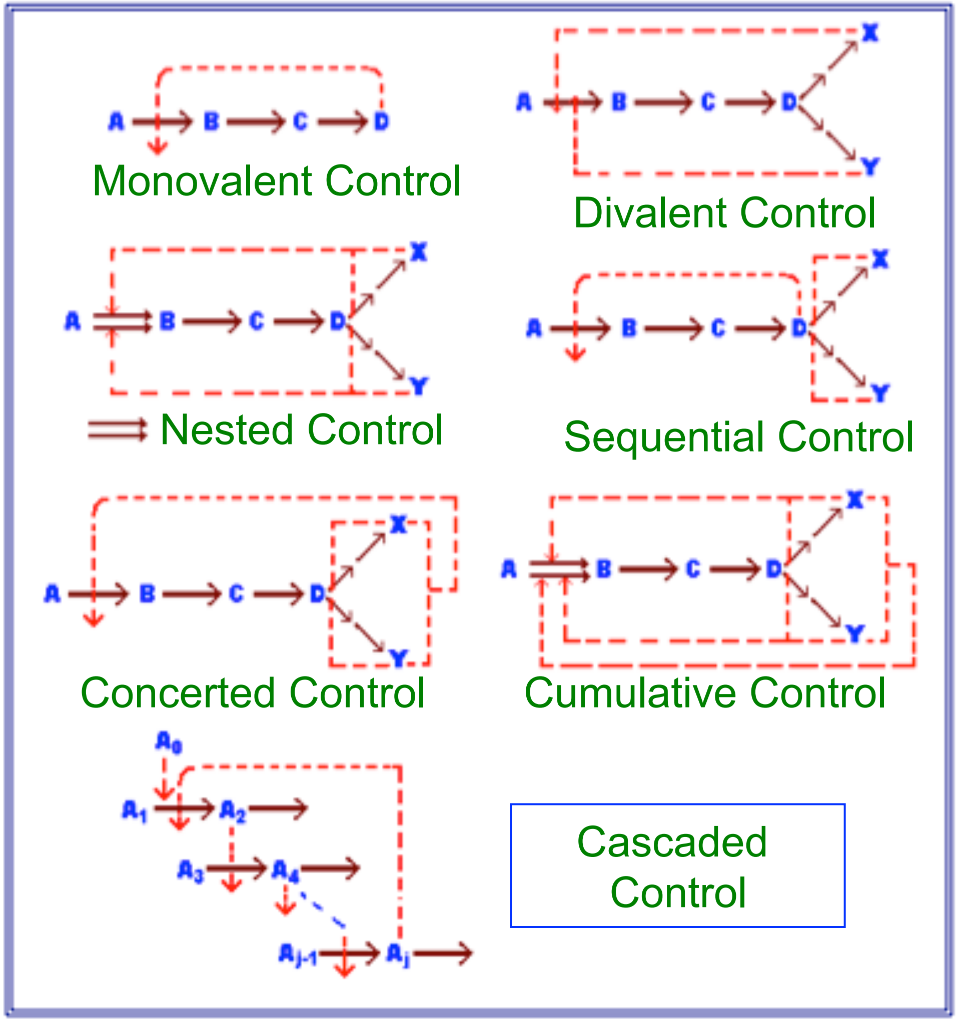
EC:4.1.3.27 → C1 → **EC:2.4.2.18** → C2 → **EC:5.3.1.24** → C3 → **EC:4.1.1.48** → C4 → **EC: 4.2.1.20a** → C5 → **EC: 4.2.1.20b**

Nodes: Reaction
Edges: Metabolite

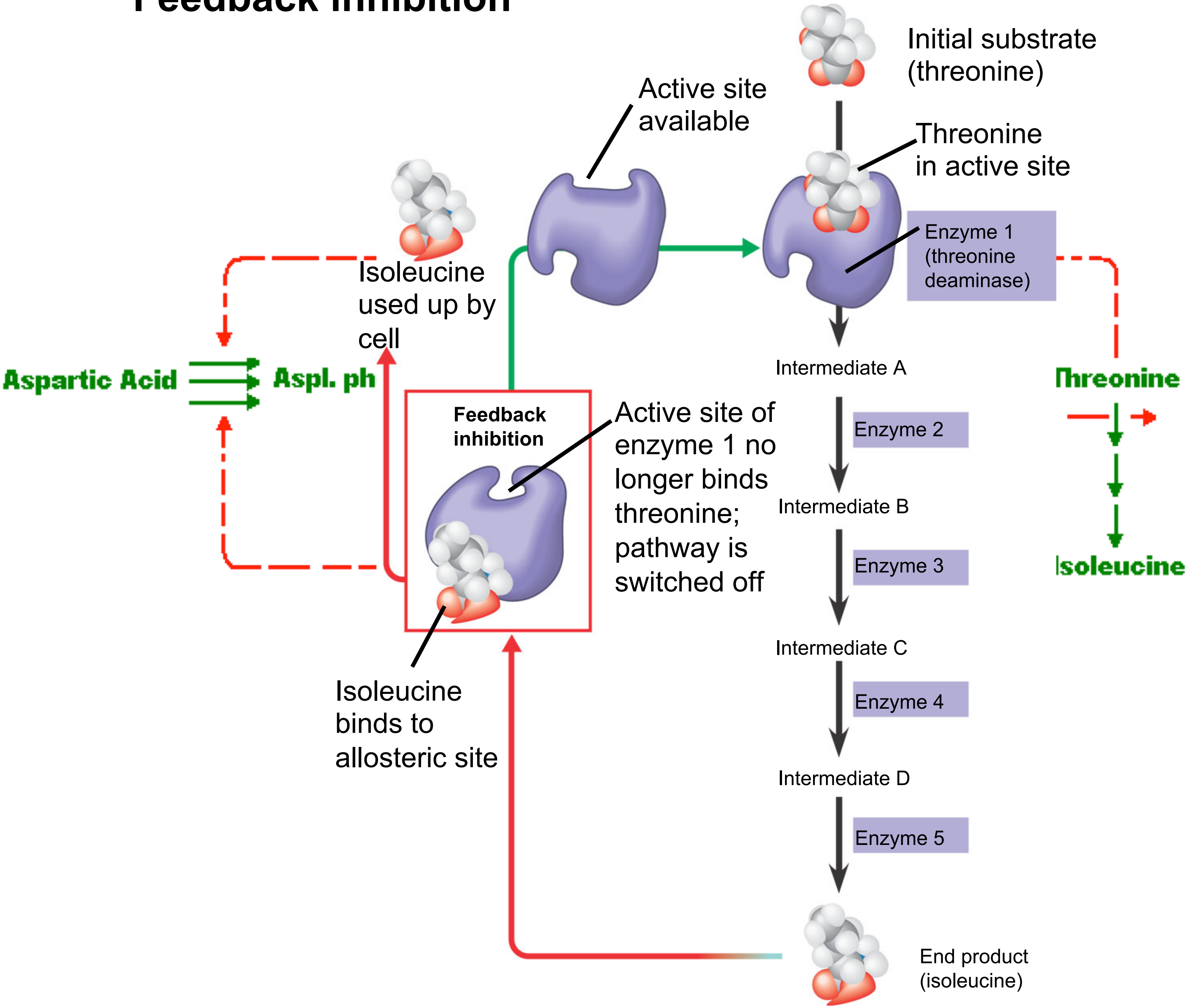
Nodes: Enzymes
Edges: Metabolite

Patterns of Regulation in Biochemical Pathways in Cells

Biochemical reactions are controlled by multiple levels of feedback processes – for different functional requirements



Feedback inhibition



Initial substrate (threonine)

Active site available

Threonine in active site

Enzyme 1 (threonine deaminase)

Intermediate A

Enzyme 2

Intermediate B

Enzyme 3

Intermediate C

Enzyme 4

Intermediate D

Enzyme 5

End product (isoleucine)

Isoleucine used up by cell

Aspartic Acid

Aspl. ph

Threonine

Isoleucine

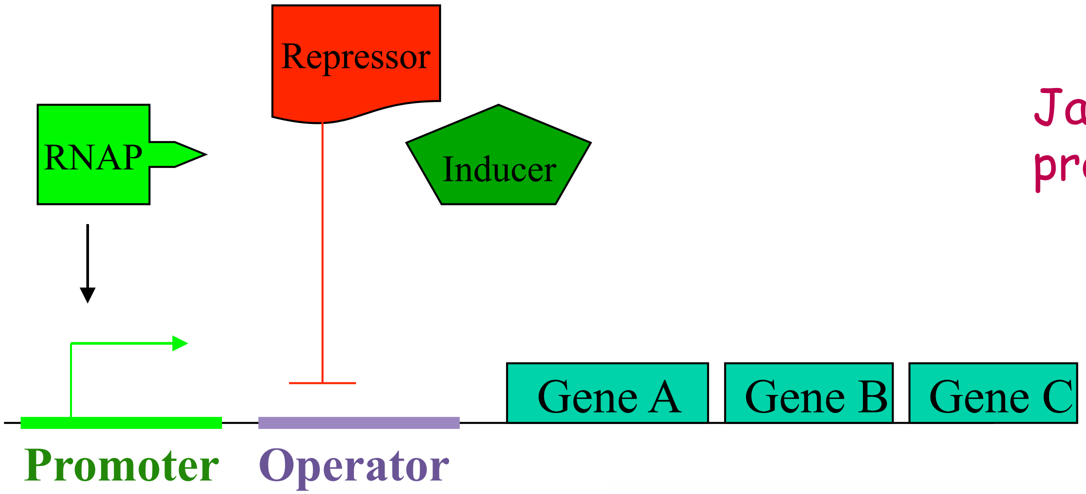
Feedback inhibition

Active site of enzyme 1 no longer binds threonine; pathway is switched off

Isoleucine binds to allosteric site

Regulation of gene expression

Organisms take decisions based on input signals and give a binary (0/1) response in some cases.


RNAP

Repressor

Inducer

Gene A

Gene B

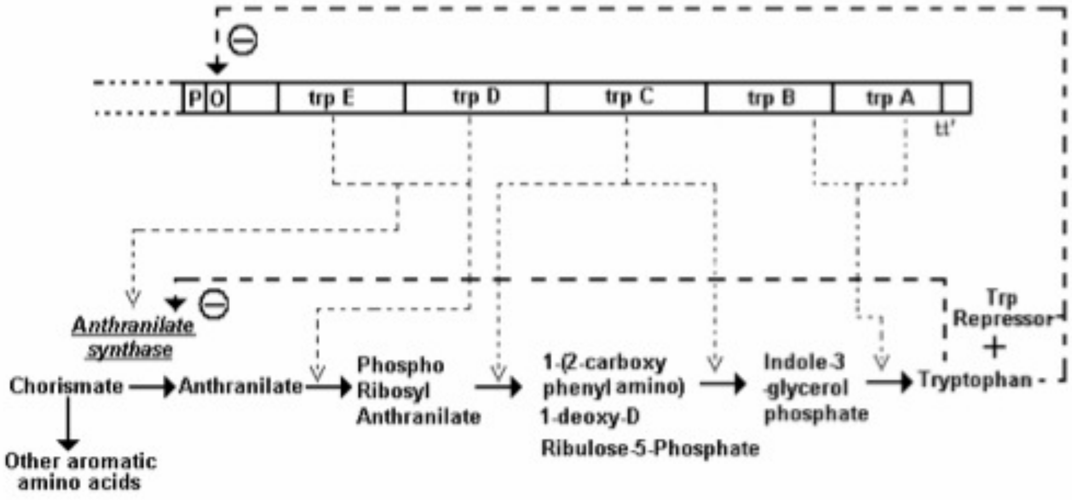
Gene C

Promoter

Operator

Jacob & Monod Model of the prokaryotic operon (1961)

Tryptophan Operon

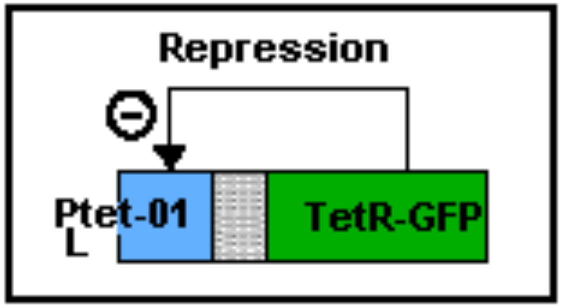


Synthetic transcriptional regulatory networks

1. Single negative feedback:

Negative feedback reduces noise.

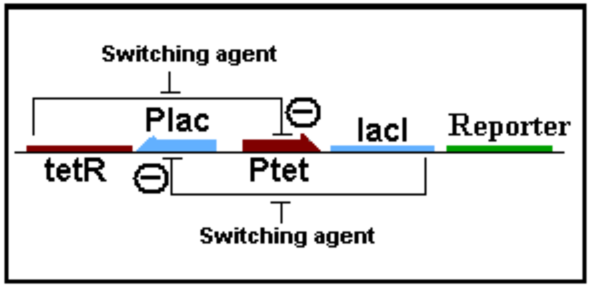
Nature(2000)

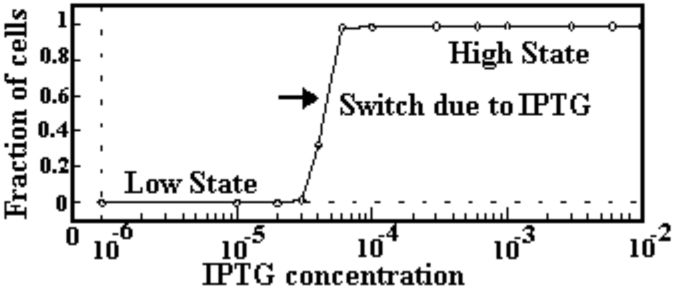


2. Two nested negative feedback:

The Toggle: *Two opposing negative feedback processes lead to switch-like behaviour.*

Nature (2000)

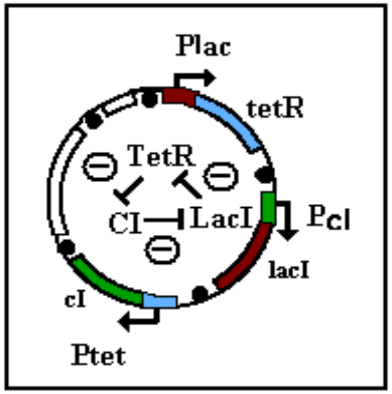


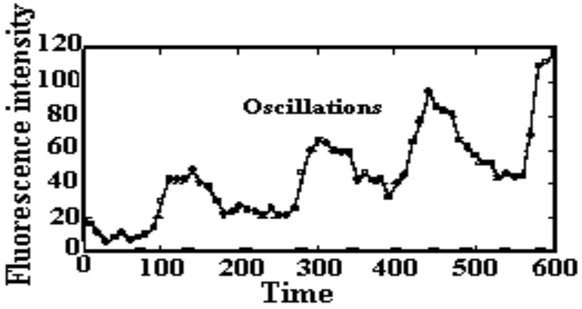


3. Three negative feedback:

The Repressilator: Oscillates due to mutual repression of the three repressors

Nature (2000)

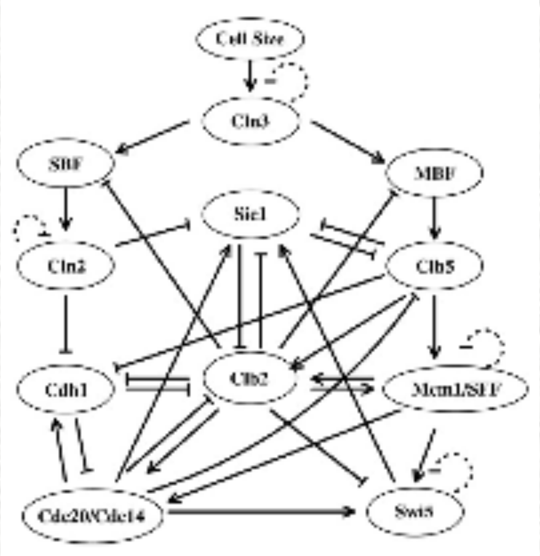


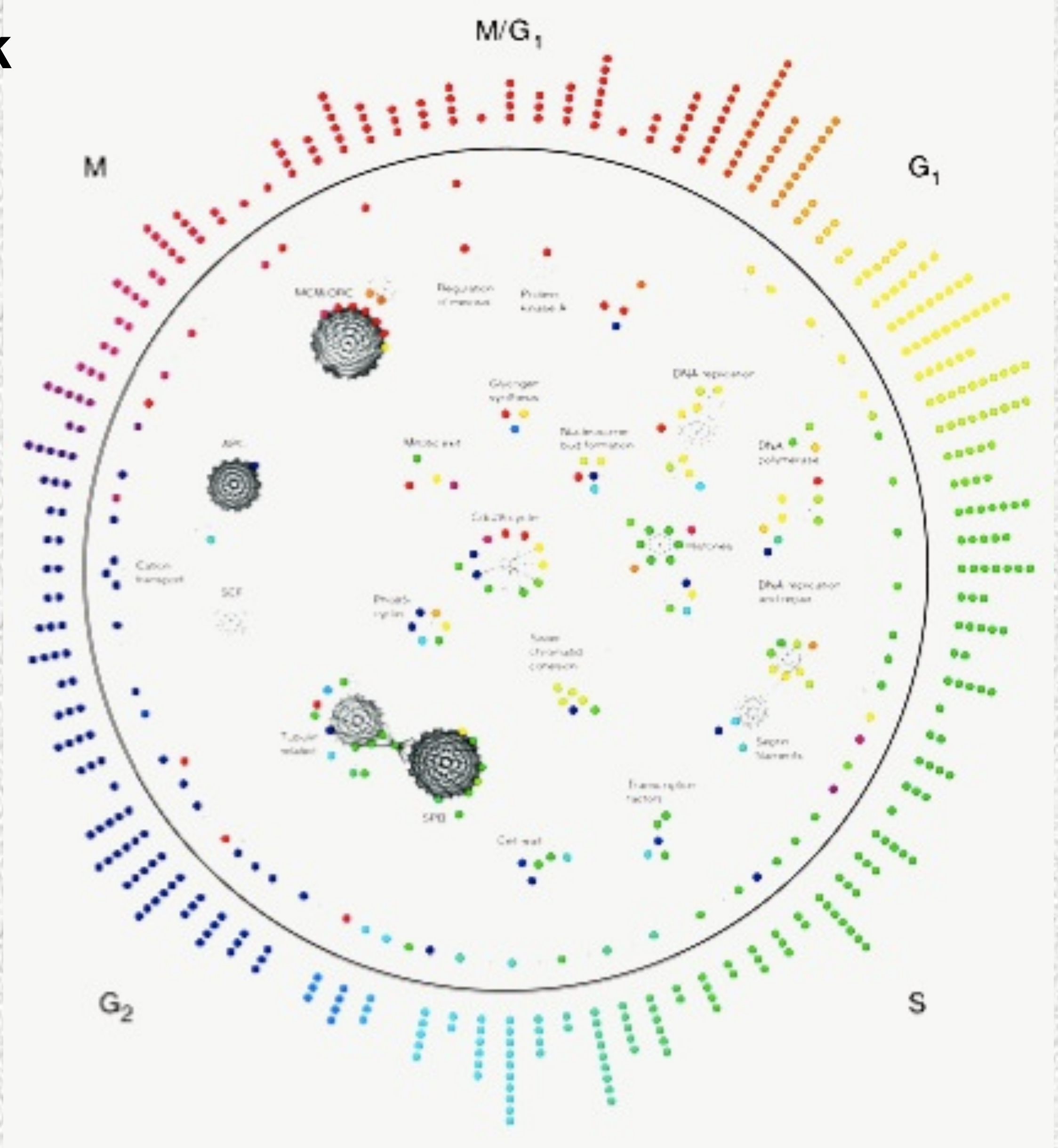


Yeast Cell Cycle Network

300 proteins (inside circle) - 184 dynamic proteins (coloured according to their time of peak expression), and 116 static proteins (in white).

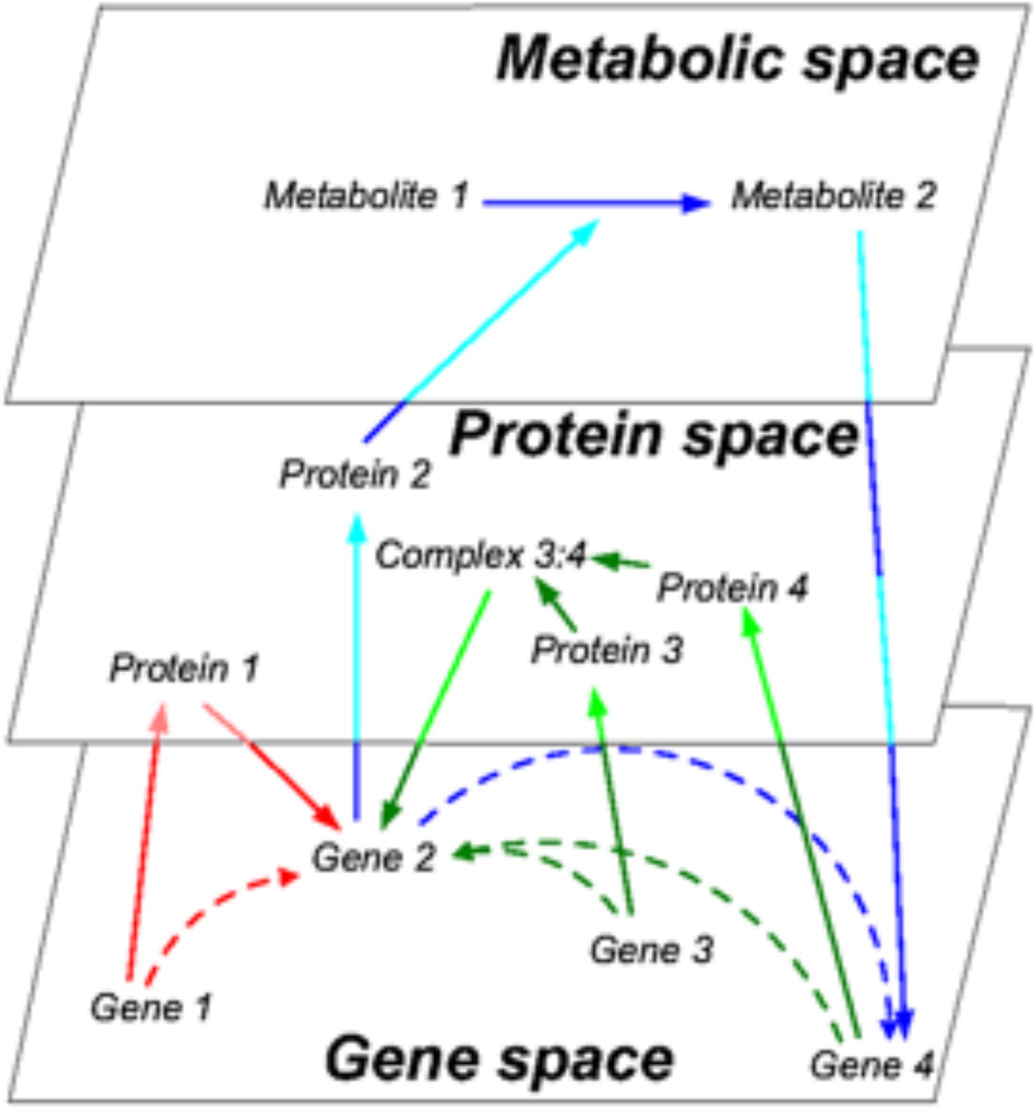
For 412 of the 600 dynamic proteins identified in the micro-array analysis, no physical interactions of sufficient reliability could be found (outside circle).





Lichtenberg, *et al* SCIENCE 2005

Li, *et al* PNAS 2004


Metabolic space
Metabolite 1
Metabolite 2
Protein space
Protein 2
Complex 3:4
Protein 4
Protein 3
Protein 1
Gene 2
Gene 3
Gene 1
Gene space
Gene 4

Design principles of transcriptional regulation networks that control gene expression

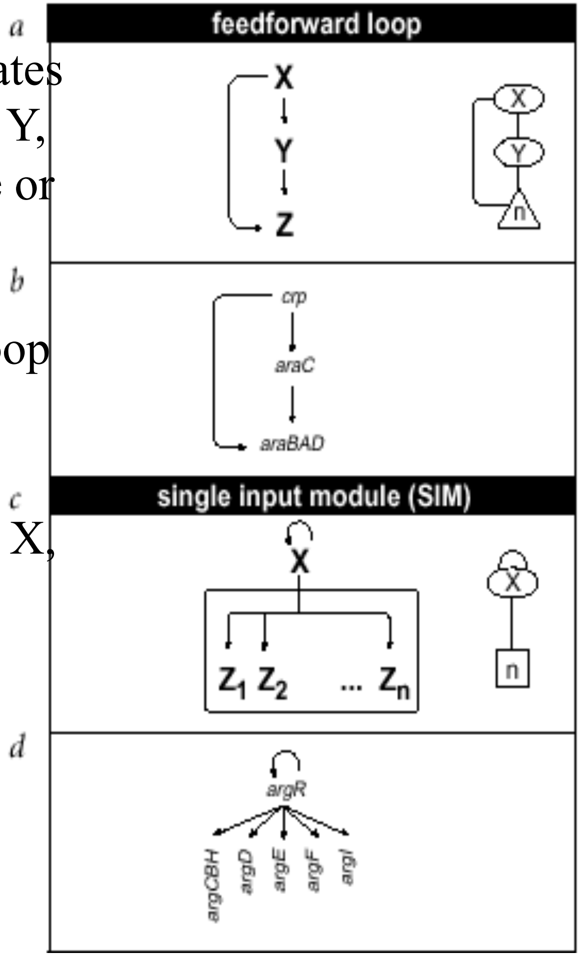
Network motifs found in the *E. coli* transcriptional regulation network

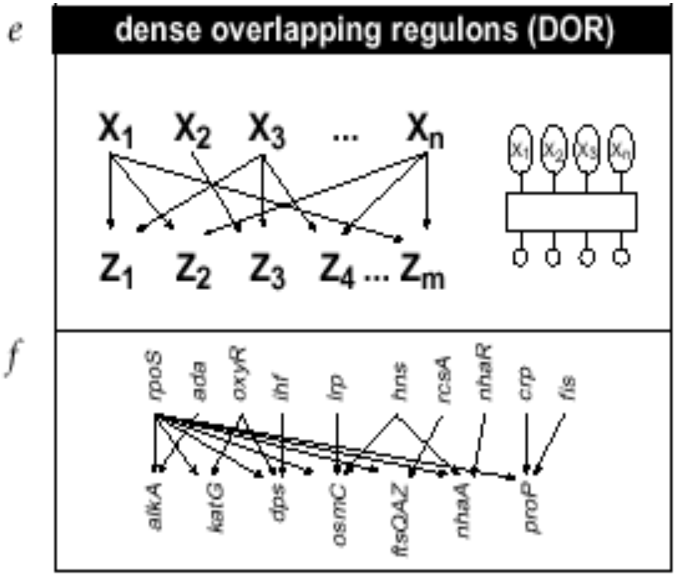
Transcription factor X regulates a second transcription factor Y, and both jointly regulate one or more operons Z 1 ...Z n

Example of a feedforward loop (L-arabinose utilization).

A single transcription factor, X, regulates a set of operons Z 1 ...Zn. X is usually auto-regulatory

Example of a SIM system (arginine biosynthesis).



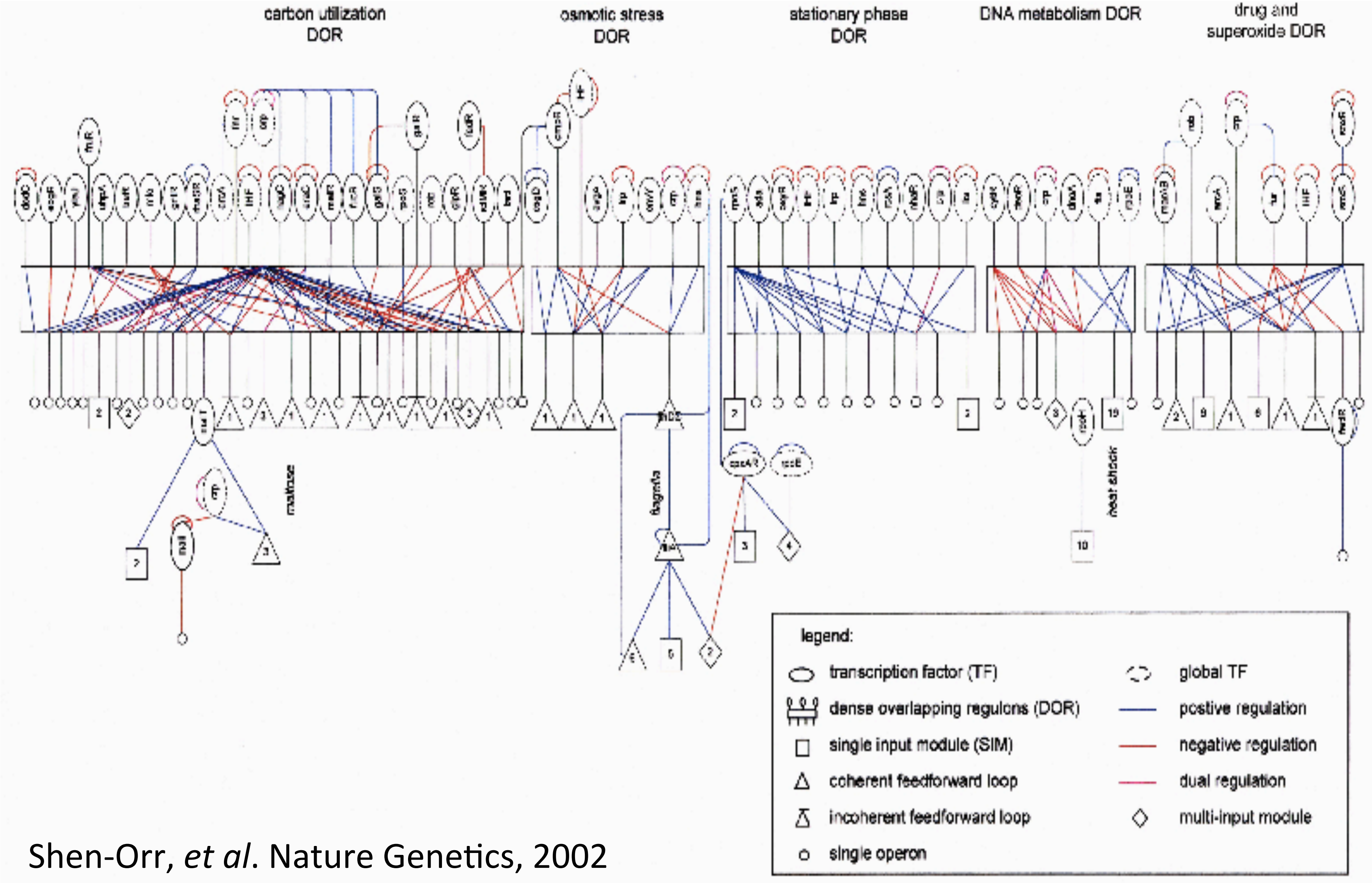


A set of operons Z_1 ...Zm are each regulated by a combination of a set of input transcription factors, X_1 ...Xn .
Example of a DOR - stationary phase response.

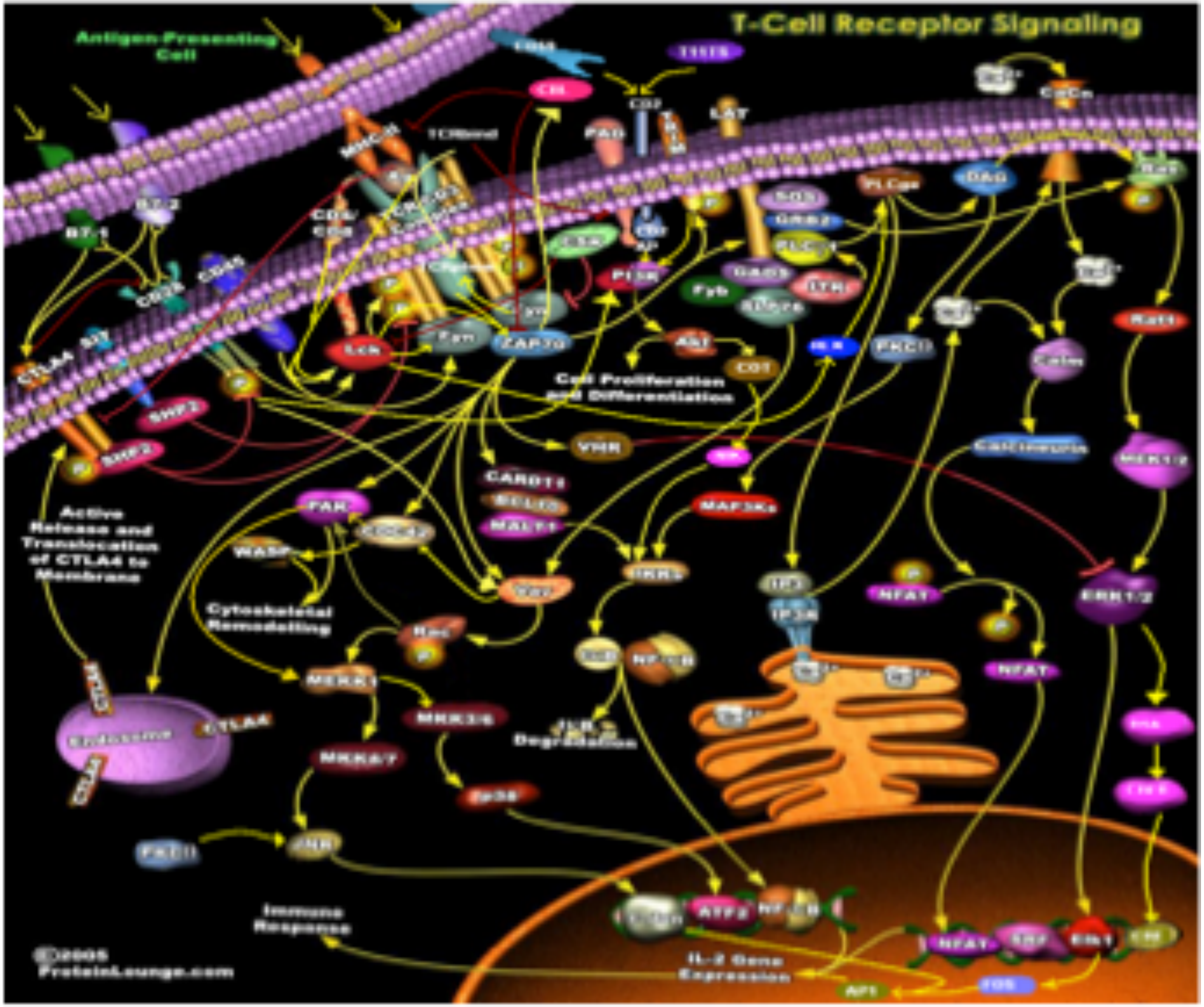
Milo et al, SCIENCE, 2002
Network Motifs: Simple Building Blocks of Complex Networks.

Global structure of the part of *E. coli* transcription network

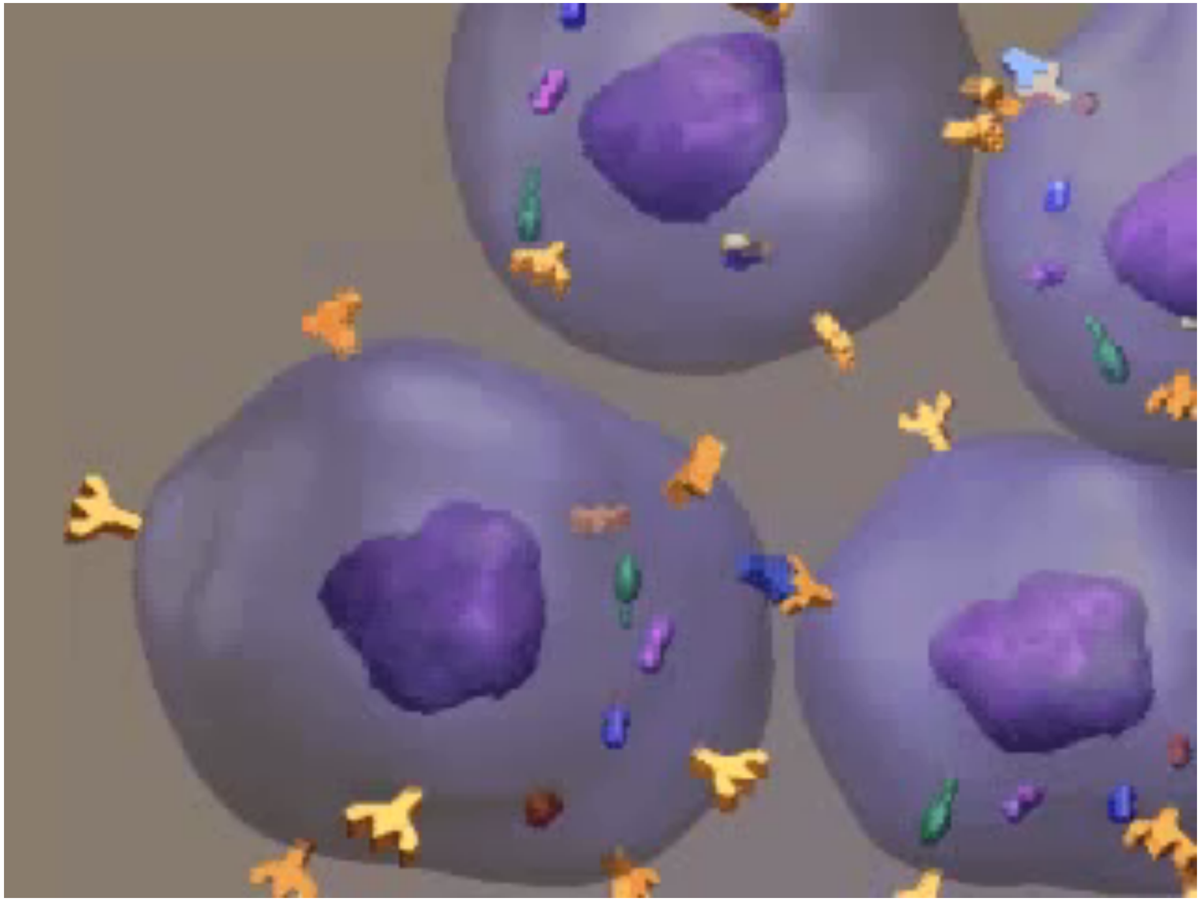
Signals from environment are read by transcription factors



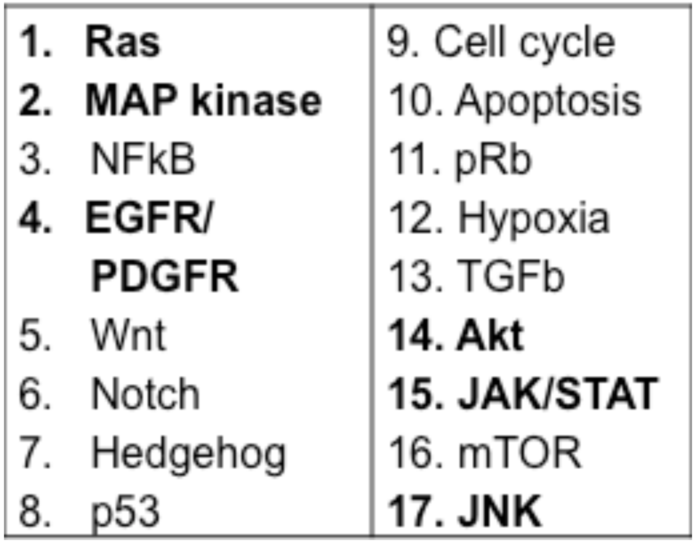
Shen-Orr, *et al*. Nature Genetics, 2002


T-Cell Receptor Signaling
Antigen Presenting Cell
CD4
TCRbind
MHC-II
CD4/ CD8
TCR-CD3 Complex
B7-2
B7-1
CD28
CD45
CTLA4
SIT
SHP2
SHP2
P
Lck
Fyn
ZAP70
CD3
Cbl
PI3K
CD2
TRIM
LAT
PAG
SOS
GRB2
PLCγ1
GADS
ITK
Fyb
SLP76
PLCγ
DAG
Ras
Raf1
MEK1/2
ERK1/2
Calm
Calcineurin
PKCθ
Akt
COT
Cell Proliferation and Differentiation
VHR
MAP3Ks
CARD11
BCL10
MALT1
IKKs
IκB
NF-κB
IκB Degradation
FAK
CDC42
WASP
Vav
Rac
P
Cytoskeletal Remodelling
MEKK1
MKK3/6
MKK4/7
p38
JNK
PKCθ
IP3
IP3R
NFAT
P
NFAT
Active Release and Translocation of CTLA4 to Membrane
Endosome
CTLA4
CTLA4
CTLA4
ATF2
NF-κB
NFAT
Elk1
IL-2 Gene Expression
AP1
FOS
Immune Response
©2005 ProteinLounge.com

SIGNAL TRANSDUCTION



Cellular signaling pathways in different cancer cell lines



1. **Ras**
2. **MAP kinase**
3. NFkB
4. **EGFR/ PDGFR**
5. Wnt
6. Notch
7. Hedgehog
8. p53
9. Cell cycle
10. Apoptosis
11. pRb
12. Hypoxia
13. TGFb
14. **Akt**
15. **JAK/STAT**
16. mTOR
17. **JNK**

Approaches:

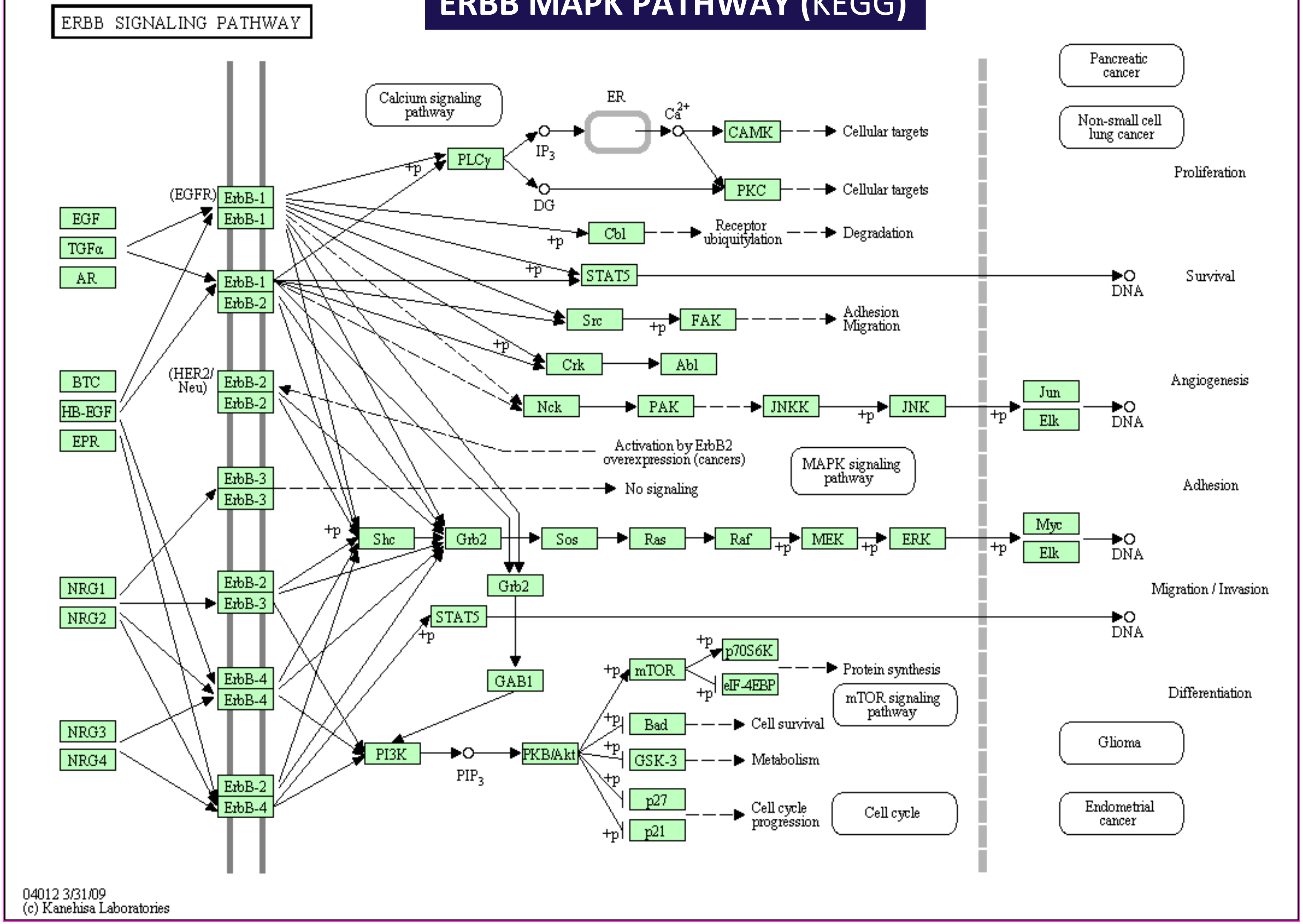
Graph theory to study networks of normal and altered pathways.

Boolean models to study signalling pathways in normal and cancer cell lines

Dynamic models to study the kinetics of regulatory processes

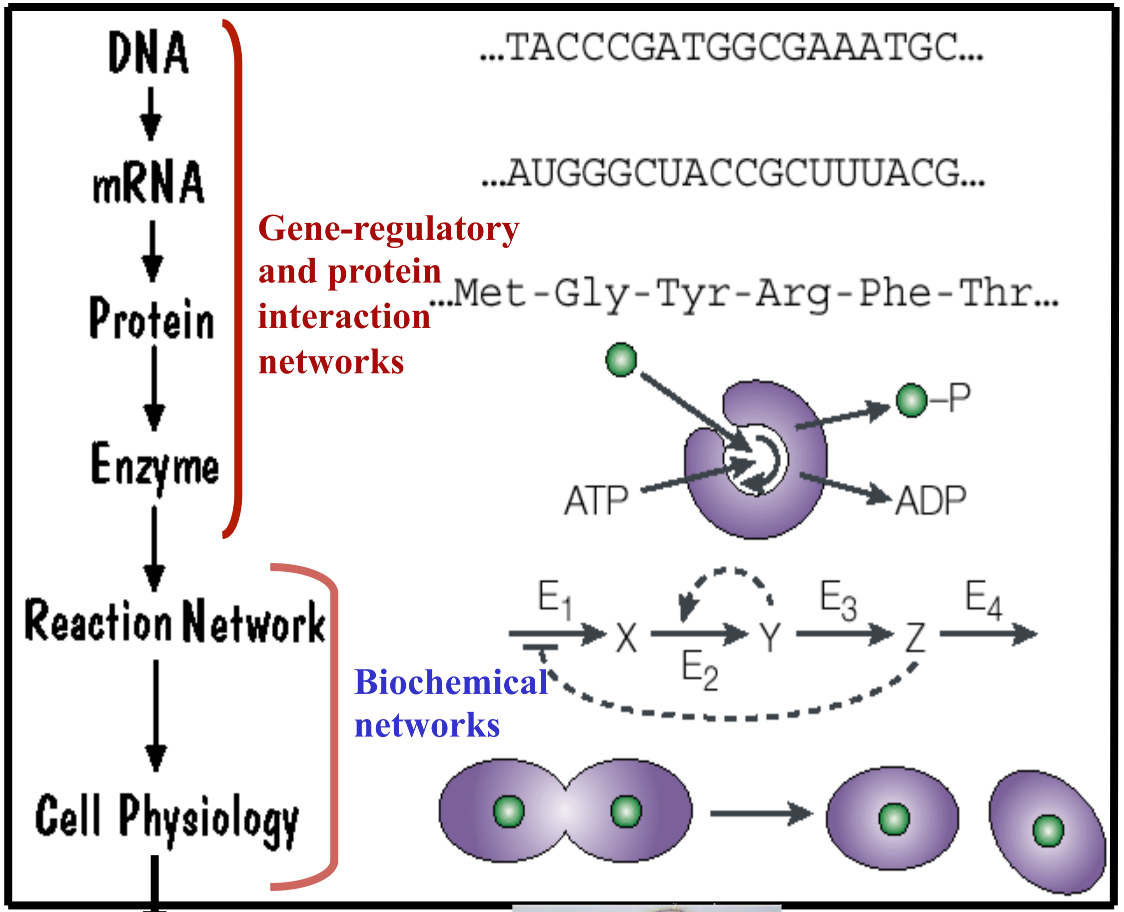
Bolds - pathways which are directly connected or related to MAPK

ERBB MAPK PATHWAY (KEGG)



Flow of Information in Biology

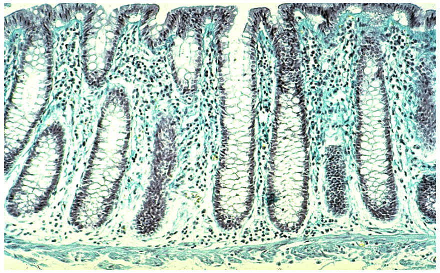
FLOW of INFORMATION



Gene-regulatory and protein interaction networks

Biochemical networks

LARGE INTESTINE



Slime mold

Multicellular systems

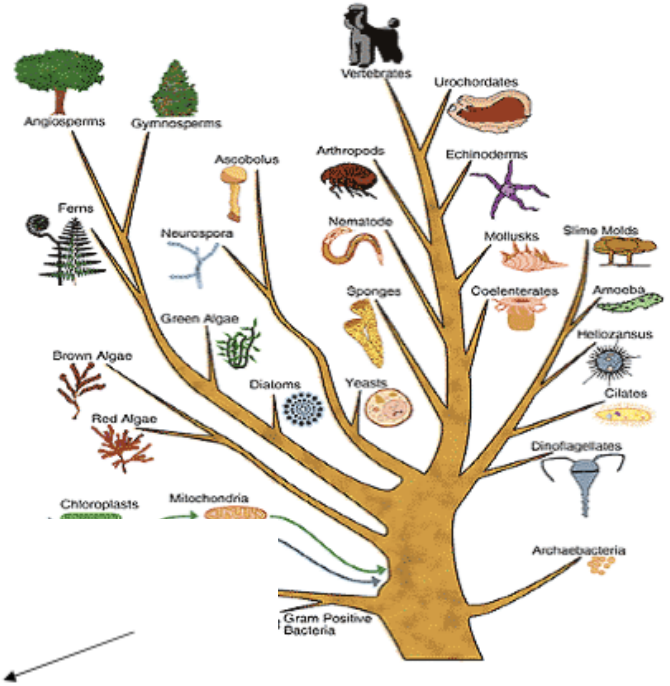
Social systems

Ecological systems

FOODWEBS,
CONTACT NETWORKS
IN EPIDEMIOLOGY

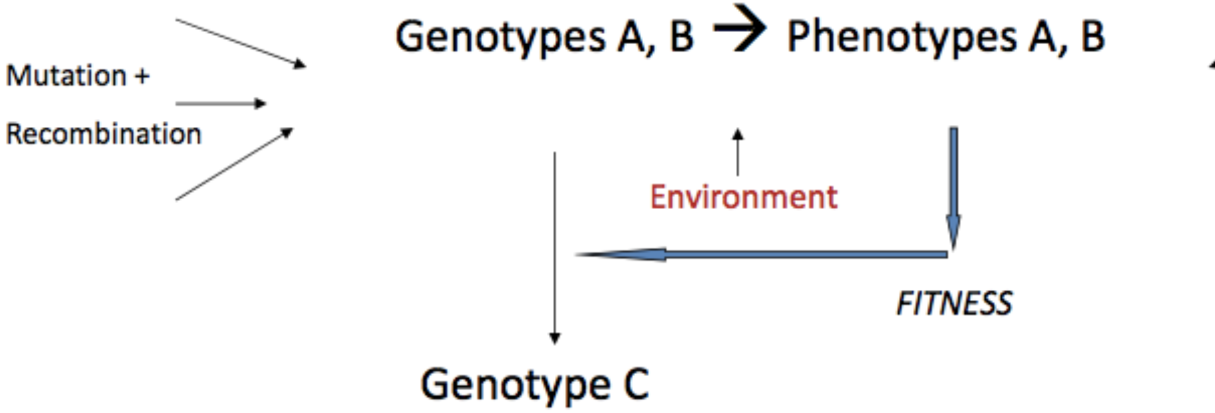
Understand the diversity of life

Number of species (estimated): 7–100 millions (identified and unidentified), including: 5–10 million bacteria;
74,000–120,000 fungi



1. Modification through descent

2. Natural selection



Genotypes A, B → Phenotypes A, B

Mutation +
Recombination

Selection

Environment

FITNESS

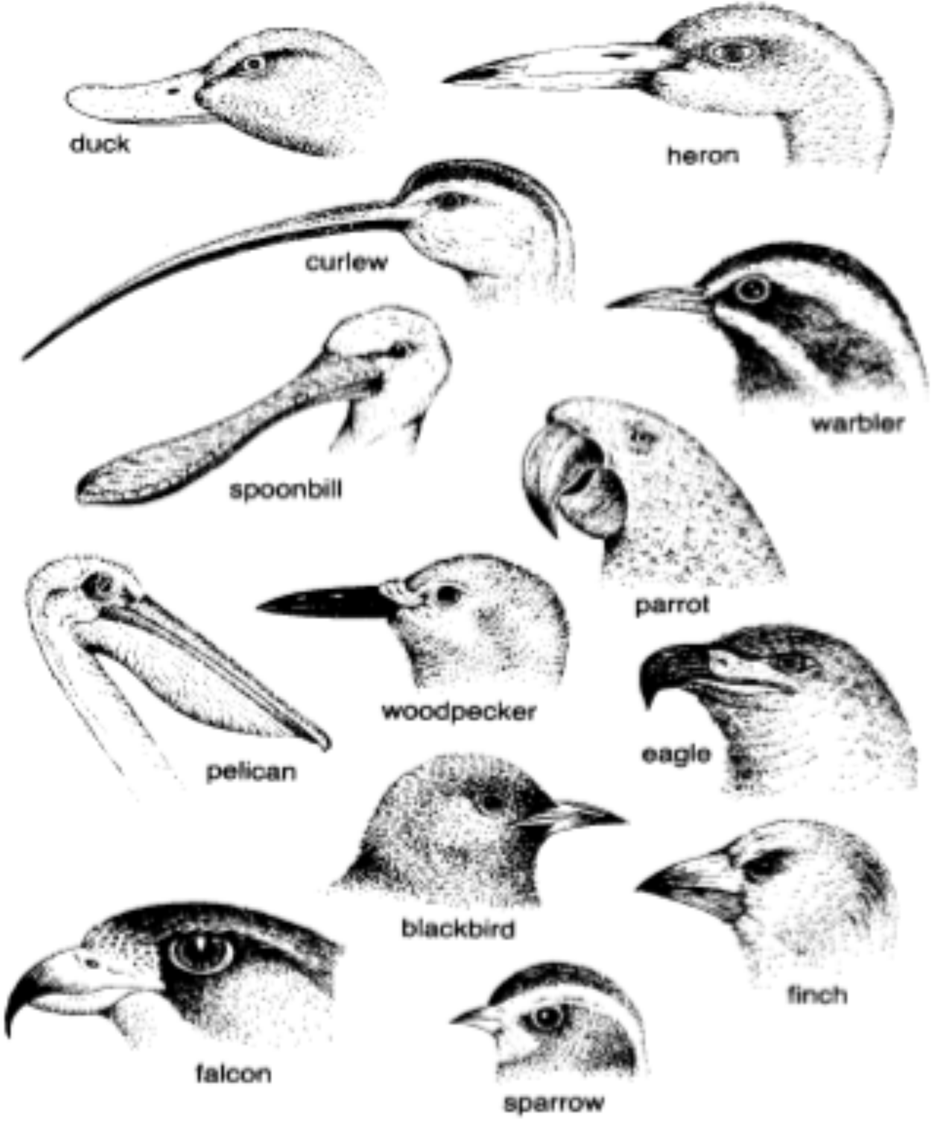
Genotype C

The genotype and environment together specify the phenotype

How do genotypes map to phenotypes?

(going from genes to traits)

Signature of natural selection: Adaptation



Adaptation works only in the short term.

Natural selection has no way of planning for the long term.

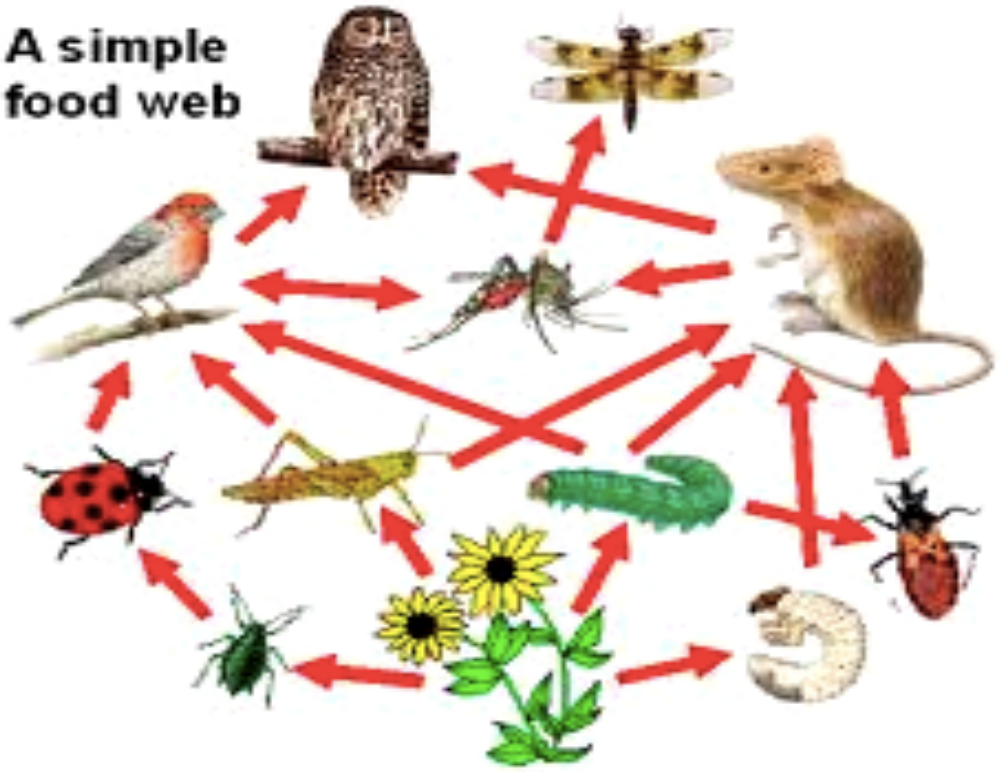
SOCIAL & ECONOMIC BEHAVIOUR -

COLLECTIVE BEHAVIOUR (Panic),
PRICE FLUCTUATIONS,
CRASHES IN STOCK MARKETS, etc

The Great Coral Reef - Ecosystem

Many species interact with each other in different ways
Many networks of interaction

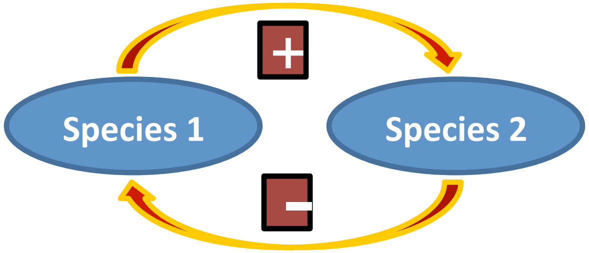
Ecological network



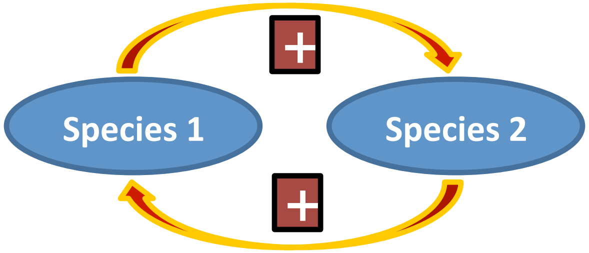
- Node- Organisms
- Edge- interaction

- The interactions among different communities of organisms are modeled.
- Effects of introducing new organisms in the network (GM crop, foreign predators, weeds/shrubs, etc)
- Effects of losing one member species in the network – how much change in biodiversity ?
- Studies in epidemiology and collective behavior of organisms

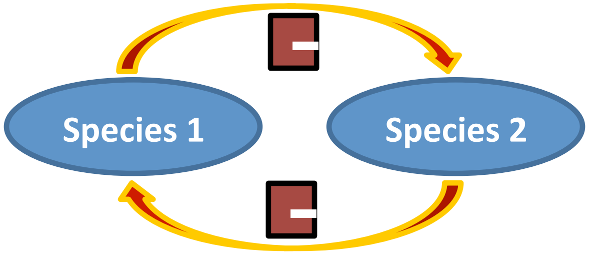
Types of ecological interactions



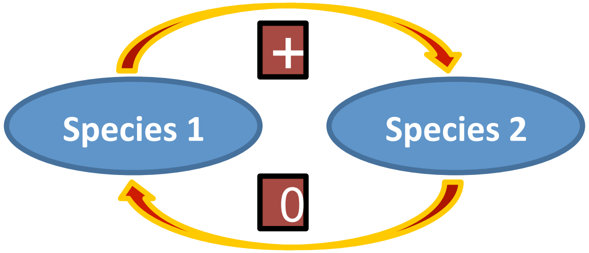
Predation



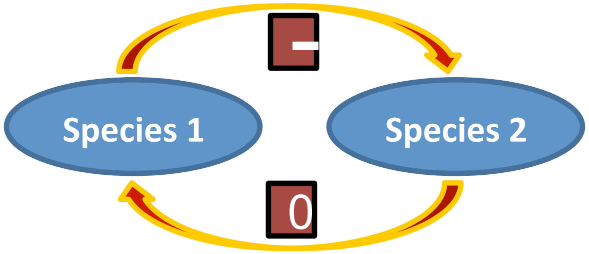
Competition



Mutualism



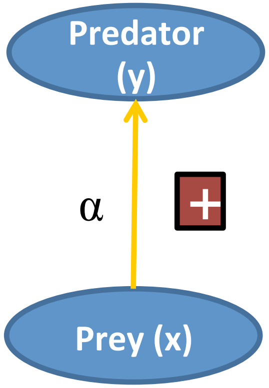
Commensalism



Ammensalism

Ecological models

Lotka–Volterra equation

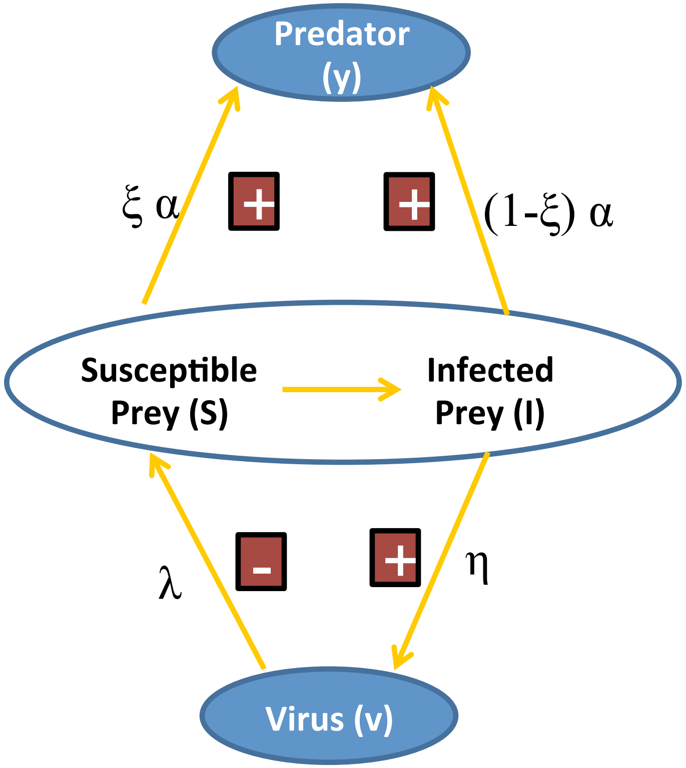


Predator (y)

α

\+

Prey (x)



Predator (y)

ξ α

\+

\+

(1-ξ) α

Susceptible Prey (S)

Infected Prey (I)

λ

\-

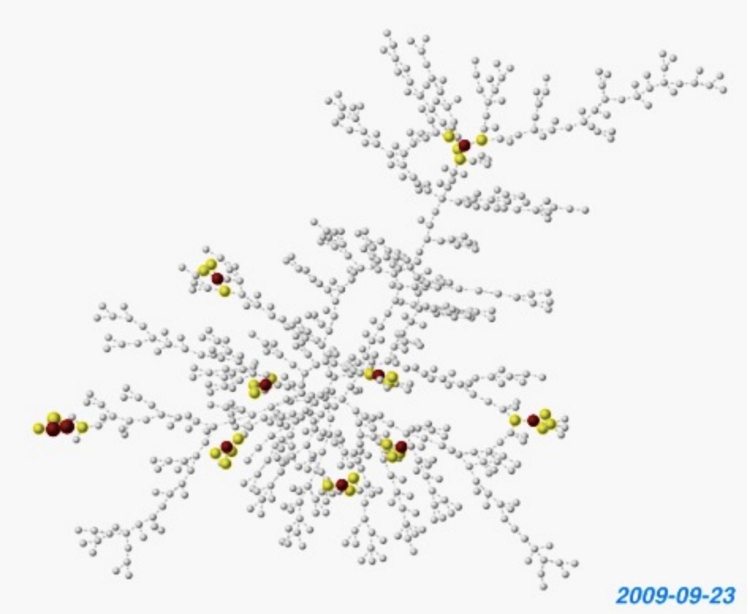
\+

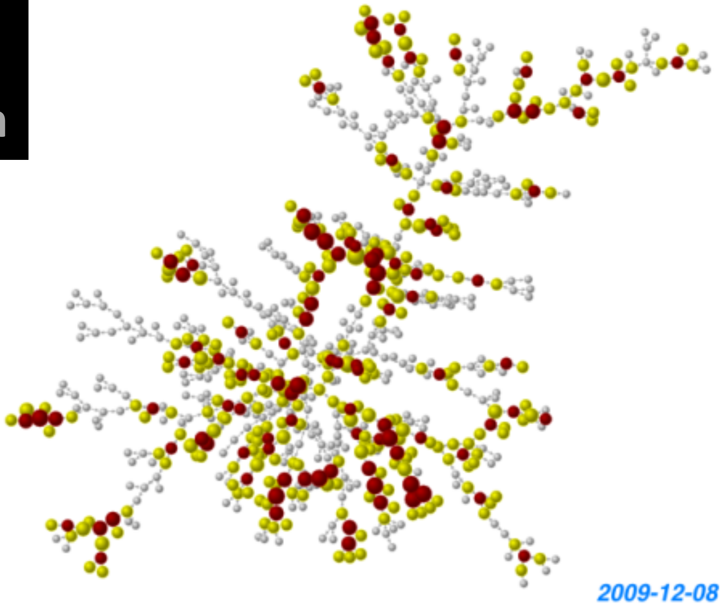
η

Virus (v)

Flu progression in friendship network

- Friends
- Infected
- General Population

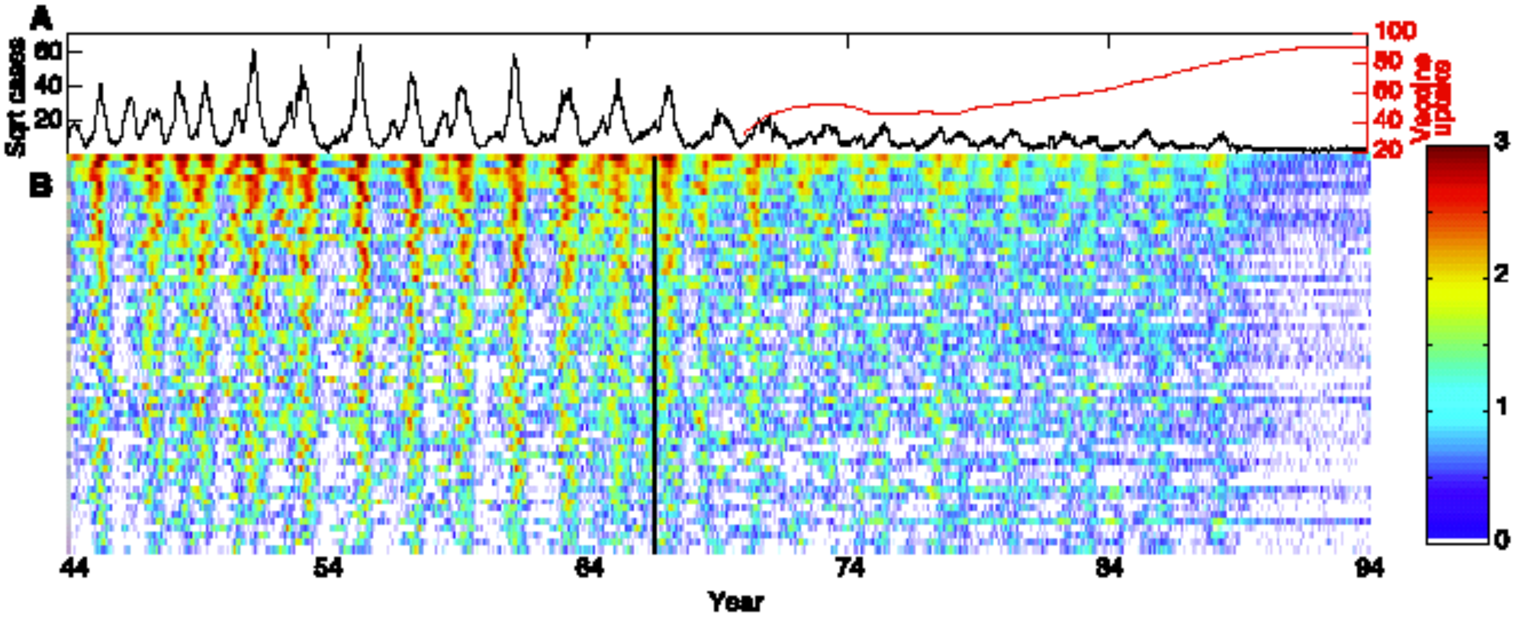

2009-09-23


2009-12-08

Infectious Diseases spread through contacts of infected individual to uninfected.

Friends, Family members form higher risk group in progression of contagious diseases.

Measles and whooping cough notifications in England and Wales from 1944 to 1994



(A) Time series for measles in London (black line) and vaccine uptake levels (percentage of infants vaccinated) for England and Wales, starting in 1968 (red line).

(B) The spatial distribution of log10 (1 + measles cases) with cities arranged in descending order of population size (from top to bottom) and colors denoting epidemic intensity (white regions highlight periods with no reported cases).

The vertical black line represent the onset of vaccination.

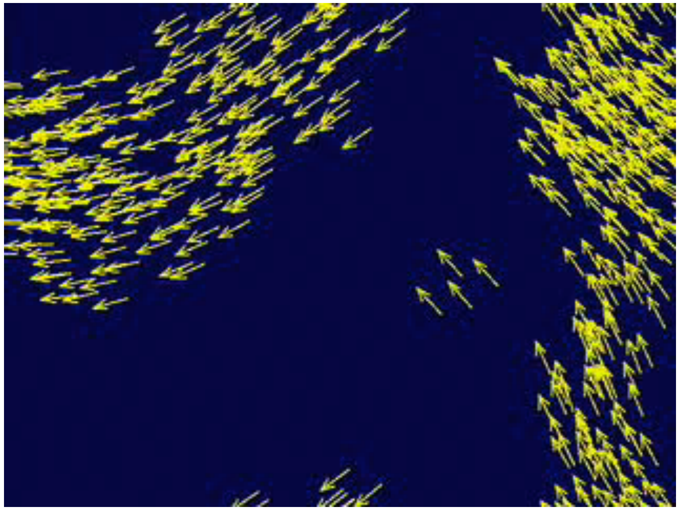
Organisation of Group Behaviour

Bird Flock, Bacterial Swarm, Fish School, Animal Herd

Interesting flocking phenomena occur when many organisms move together and each try to follow its neighbours

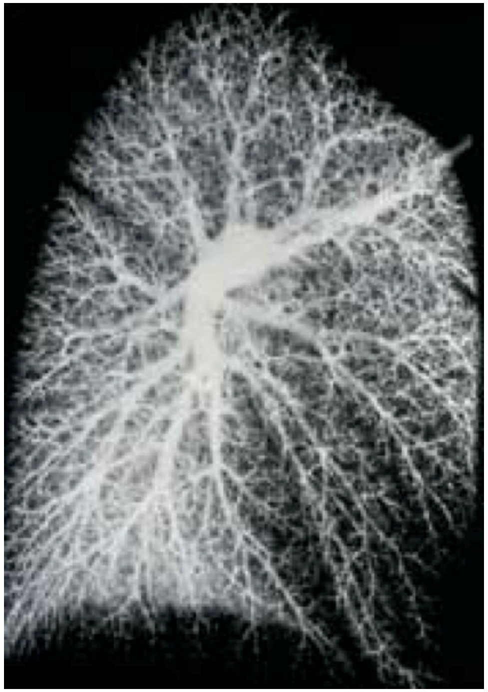
Global pattern formation based on local information

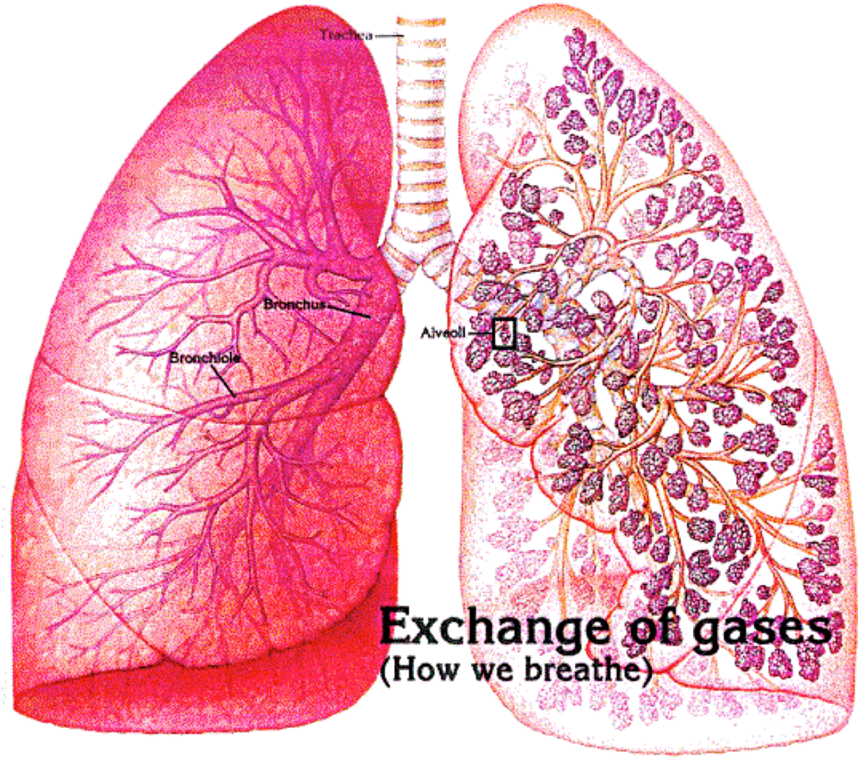
The transition which can be observed as a function of the perturbations is unique to the system



From Tamas Viscek's website

Patterns of tissue or organ structure- helps in functions



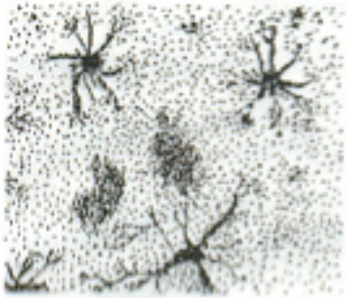


The lungs have an extensive network of blood vessels. This aids in excellent blood supply that is needed to transport oxygen away from the lungs efficiently.

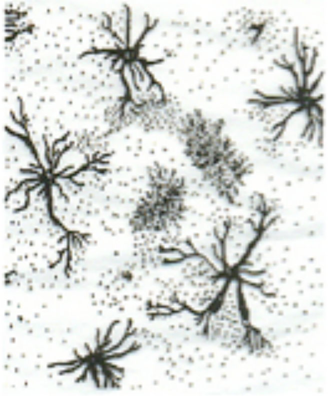
Spatio-Temporal Patterns
change lead to developmental irregularities

social amoebae

Free-living cells - eat and reproduce



Cells aggregate (signal (cAMP) relay)

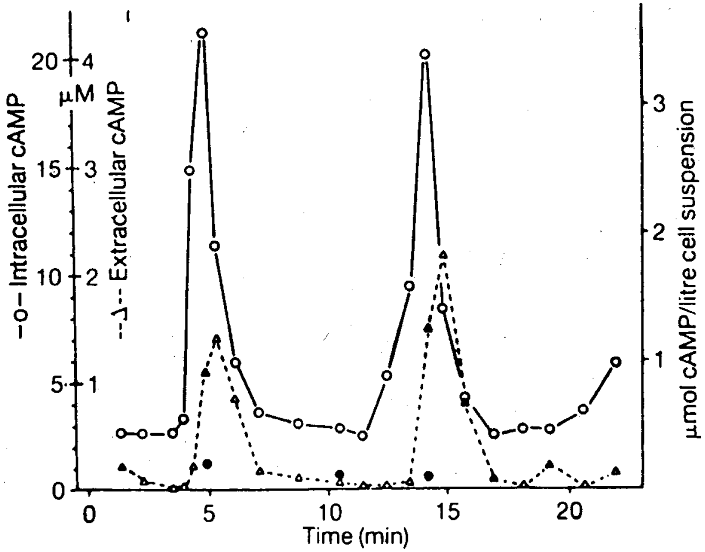


Large aggregation centres formed

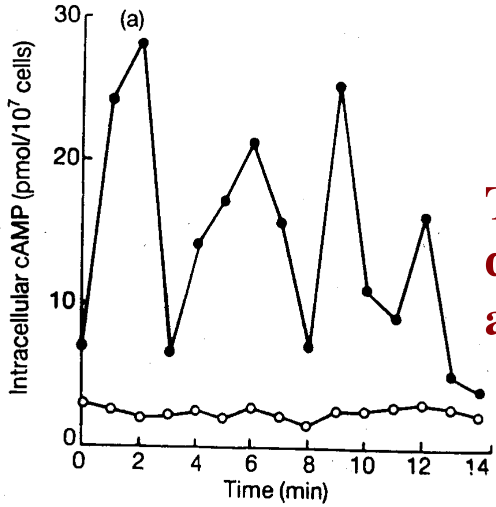
Mound of cells form slug

Fruiting body with stalk and spore cells

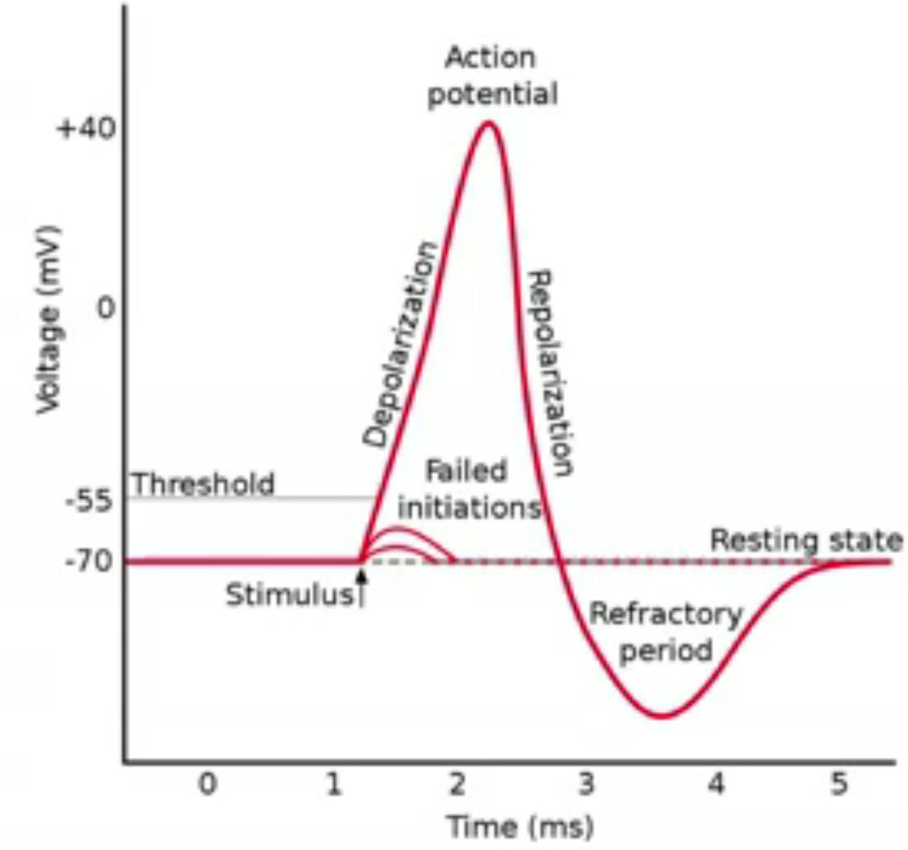
Active communication and interaction among the cells

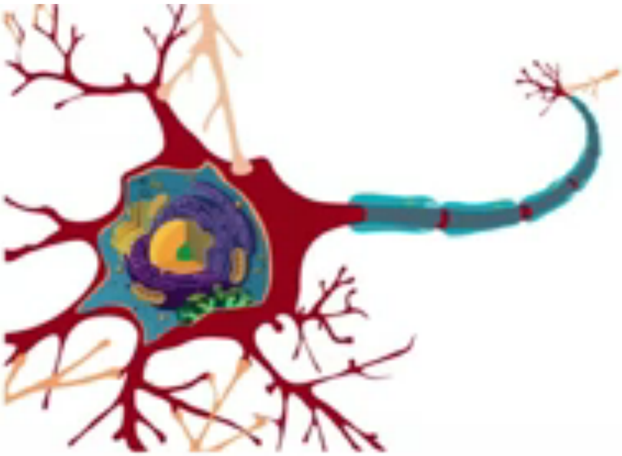


6.5 Mutant Fr17: *autonomous chaos?*



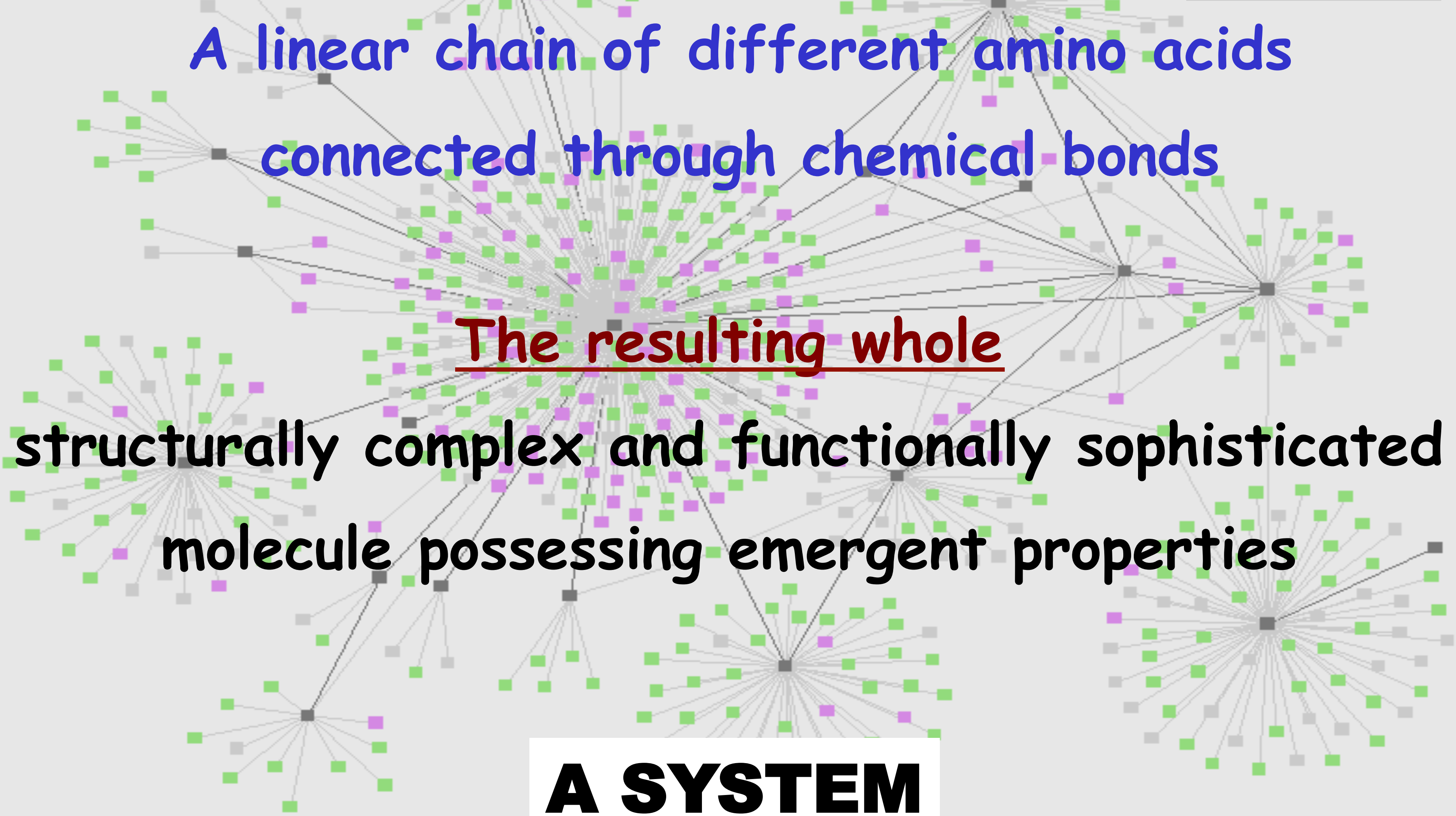
This mutant strain does not form slug and fruiting body


Action potential
+40
0
-55
-70
Voltage (mV)
Depolarization
Repolarization
Threshold
Failed initiations
Resting state
Stimulus
Refractory period
0
1
2
3
4
5
Time (ms)

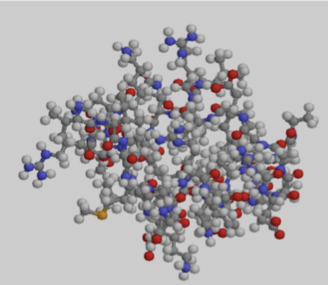


Synapse activity in neuronal network

PROTEINS
AS
NETWORKS



PROTEIN



A linear chain of different amino acids connected through chemical bonds

The resulting whole

structurally complex and functionally sophisticated molecule possessing emergent properties

A SYSTEM

What about Proteins ?

- Proteins are synthesised in the cell as linear chains of amino acids having thousands of atoms and hence millions of possible inter-atomic interactions
- Protein chain folds through *short and long range interactions* into secondary and tertiary (and quarternary) structures.
- Proteins acquire their three-dimensional structures in surprisingly short time (within sec/min).
- Proteins perform sophisticated biochemical functions specified by their detailed 3-D structures.

The three-dimensional structures of proteins can be studied as networks of amino acids whose large scale features may give indications of their biophysical properties.

The polypeptide chains that make up proteins have thousands of atoms and hence millions of possible inter-atomic interactions.

Does the resulting complexity make prediction of protein structure and protein-folding mechanisms nearly impossible ?

The fundamental physics underlying folding may be much simpler than this complexity would allude to:
Folding rates and mechanisms appear to be largely determined by the topology of the native (folded) state.

New methods have shown great promise in predicting protein-folding mechanisms and their three-dimensional structures.

The challenge is to improve these models so that they can contribute to the interpretation of genome sequence information.

D. Baker NATURE (2000)

We use Network Analysis, based on Graph Theory, to construct "**Contact Networks**" from the native structures of the Proteins - as **networks of their constituent amino acids**.

We study various **network parameters** of these protein of different structural classes, which offer **insight into the structural organisation and correlate them to biophysical properties** of the proteins, such as, the folding kinetics.

We use these **global parameters** of the protein networks to identify **functionally important residues, and visualise structural perturbations occurring during ligand-binding and allosteric regulation.**

DATA & NETWORK ANALYSES

DATA:

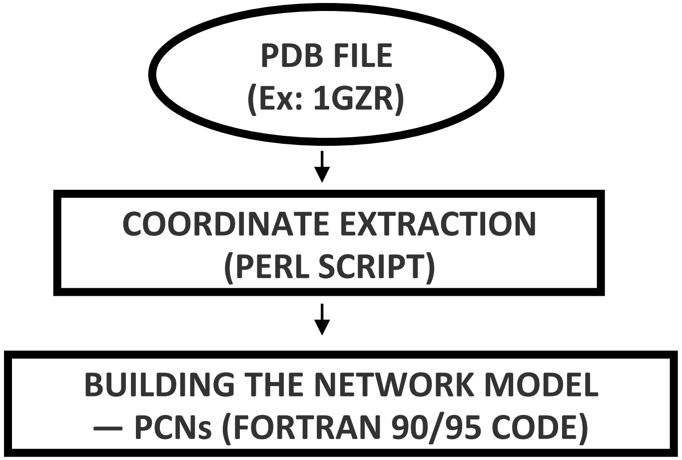
Protein Data Bank (PDB).

DATA ACQUISITION and NETWORK ANALYSES:

Fortran 90/95, Perl

ANALYSES and VISUALIZATION:

MATLAB, GNUPLOT, Graphviz, SPSS, Pajek

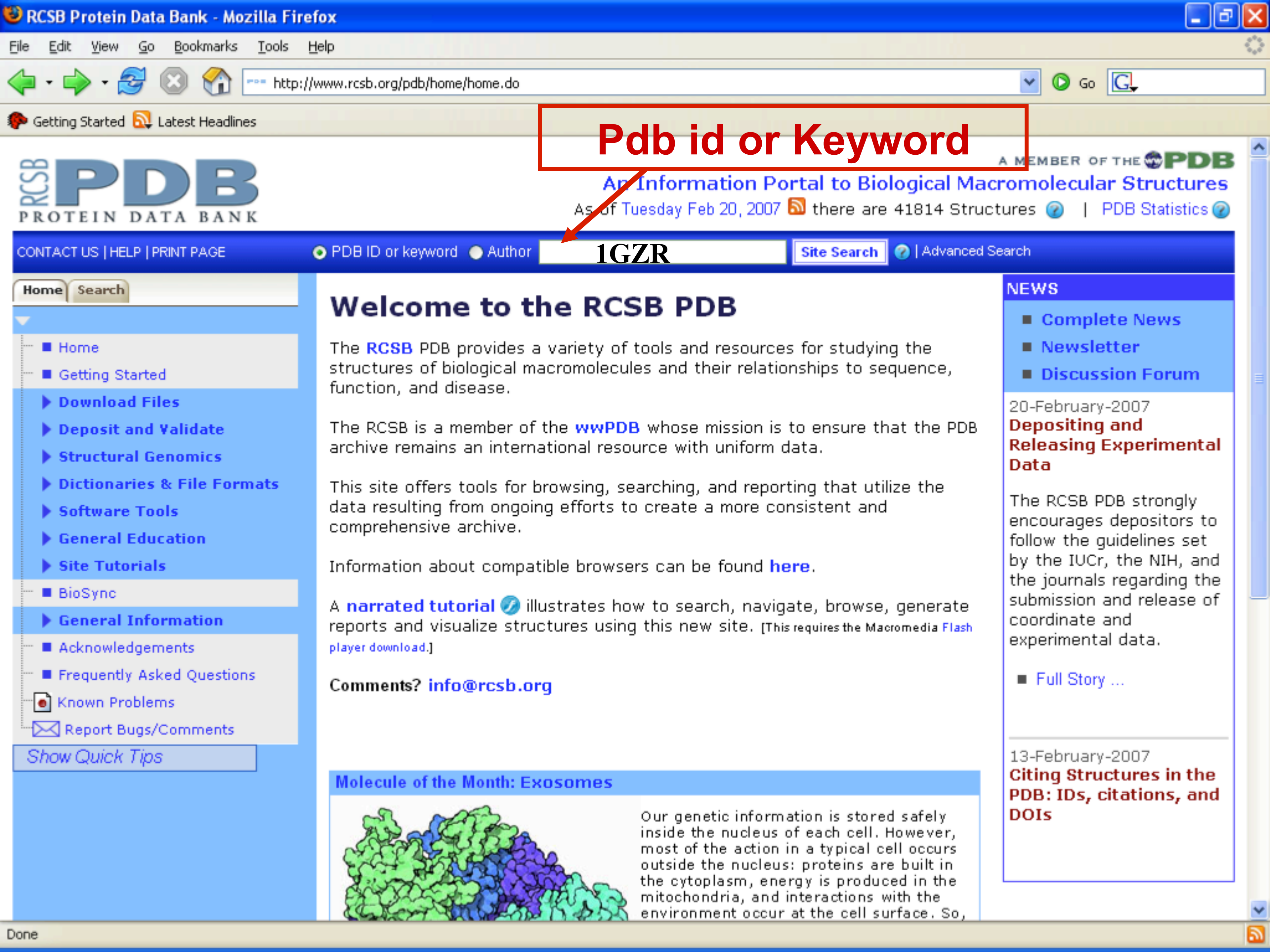


PDB FILE
(Ex: 1GZR)

COORDINATE EXTRACTION
(PERL SCRIPT)

BUILDING THE NETWORK MODEL
— PCNs (FORTRAN 90/95 CODE)

Pdb id or Keyword



An Information Portal to Biological Macromolecular Structures

As of Tuesday Feb 20, 2007 there are 41814 Structures | PDB Statistics

Welcome to the RCSB PDB

The RCSB PDB provides a variety of tools and resources for studying the structures of biological macromolecules and their relationships to sequence, function, and disease.

The RCSB is a member of the wwPDB whose mission is to ensure that the PDB archive remains an international resource with uniform data.

This site offers tools for browsing, searching, and reporting that utilize the data resulting from ongoing efforts to create a more consistent and comprehensive archive.

Information about compatible browsers can be found here.

A narrated tutorial illustrates how to search, navigate, browse, generate reports and visualize structures using this new site. [This requires the Macromedia Flash player download.]

Comments? info@rcsb.org

Molecule of the Month: Exosomes

Our genetic information is stored safely inside the nucleus of each cell. However, most of the action in a typical cell occurs outside the nucleus: proteins are built in the cytoplasm, energy is produced in the mitochondria, and interactions with the environment occur at the cell surface. So,

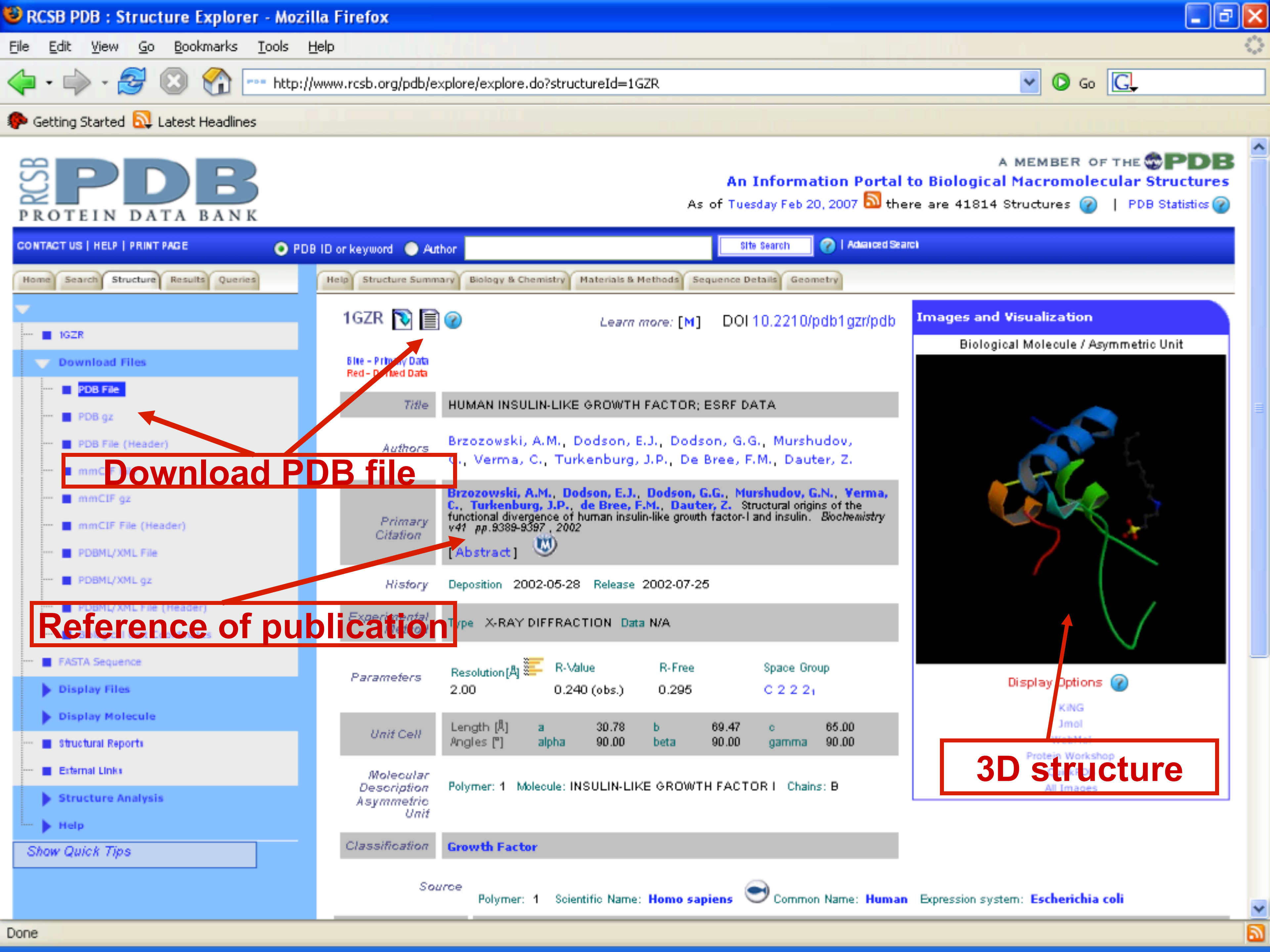
20-February-2007

Depositing and Releasing Experimental Data

The RCSB PDB strongly encourages depositors to follow the guidelines set by the IUCr, the NIH, and the journals regarding the submission and release of coordinate and experimental data.

13-February-2007

Citing Structures in the PDB: IDs, citations, and DOIs



http://www.rcsb.org/pdb/explore/explore.do?structureId=1GZR

An Information Portal to Biological Macromolecular Structures

As of Tuesday Feb 20, 2007 there are 41814 Structures | PDB Statistics

○ PDB ID or keyword ○ Author

1GZR Learn more: [M] DOI 10.2210/pdb1gzr/pdb

Title	HUMAN INSULIN-LIKE GROWTH FACTOR; ESRF DATA
Authors	Brzozowski, A.M., Dodson, E.J., Dodson, G.G., Murshudov, G., Verma, C., Turkenburg, J.P., De Bree, F.M., Dauter, Z.
Primary Citation	**Brzozowski, A.M.**, **Dodson, E.J.**, **Dodson, G.G.**, **Murshudov, G.N.**, **Verma, C.**, **Turkenburg, J.P.**, **de Bree, F.M.**, **Dauter, Z.** Structural origins of the functional divergence of human insulin-like growth factor-I and insulin. *Biochemistry v41 pp.9389-9397 , 2002* [Abstract]
History	Deposition 2002-05-28 Release 2002-07-25
Experimental Method	Type X-RAY DIFFRACTION Data N/A

Parameters	Resolution[Å]	R-Value	R-Free	Space Group
	2.00	0.240 (obs.)	0.295	$C\ 2\ 2\ 2_1$

Unit Cell							
Length [Å]	a	30.78	b	69.47	c	65.00
Angles [°]	alpha	90.00	beta	90.00	gamma	90.00

Molecular Description Asymmetric Unit	Polymer: 1 Molecule: INSULIN-LIKE GROWTH FACTOR I Chains: B
Classification	**Growth Factor**
Source	Polymer: 1 Scientific Name: **Homo sapiens** Common Name: **Human** Expression system: **Escherichia coli**

Download PDB file

Reference of publication

3D structure

PROTEIN NETWORK MODELS

Protein Contact Network (PCN)
is based on spatial contacts made by residues in the polypeptide chain.

Coarse-grained model:
Any two residues are said to be in spatial contact, if the C-alpha atoms are within a threshold distance; Rc ≤ 8 Å.

(Results are independent of Rc, for 5 Å ≤ Rc ≤ 10 Å)

All atom networks are also built for studying certain kinds of problems

1GZR - *HUMAN INSULIN-LIKE GROWTH FACTOR*

A.Brzozowski, et al. STRUCTURAL ORIGINS OF THE FUNCTIONAL DIVERGENCE OF HUMAN INSULIN-LIKE GROWTH FACTOR-I AND INSULIN. ***BIOCHEMISTRY Vol. 41 p 9389 2002***

GLY PRO **GLU** **THR** LEU CYS GLY ALA GLU LEU VAL ASP ALA LEU
GLN PHE VAL CYS GLY ASP ARG GLY PHE TYR PHE ASN LYS PRO
THR GLY TYR GLY SER SER SER ARG ARG ALA PRO GLN THR GLY
ILE VAL ASP GLU CYS CYS PHE ARG SER CYS ASP LEU ARG ARG

LEU GLU MET TYR CYS ALA PRO LEU LYS PRO ALA LYS SER ALA

Crystallographic co-ordinates

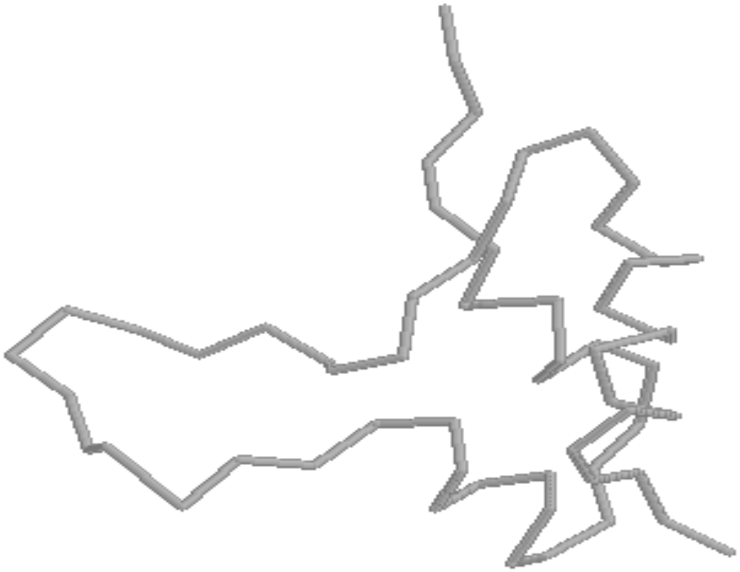
```
ATOM      1  N    GLU B   3    6.081  22.338  18.580  N
ATOM      2  CA   GLU B   3    4.955  21.483  19.072  C
ATOM      3  C    GLU B   3    5.461  20.314  19.918  C
ATOM      4  O    GLU B   3    4.726  19.344  20.160  O
ATOM      5  CB   GLU B   3    4.128  20.968  17.888  C
ATOM      6  CG   GLU B   3    3.367  19.676  18.151  C
ATOM      7  CD   GLU B   3    1.964  19.689  17.558  C
ATOM      8  OE1  GLU B   3    1.766  20.306  16.484  O
ATOM      9  OE2  GLU B   3    1.053  19.082  18.168  O
ATOM     10  N    THR B   4    6.709  20.411  20.369  N
ATOM     11  CA   THR B   4    7.423  19.262  20.919  C
ATOM     12  C    THR B   4    8.077  19.589  22.263  C
ATOM     13  O    THR B   4    7.954  20.701  22.740  O
ATOM     14  CB   THR B   4    8.453  18.753  19.905  C
ATOM     15  OG1  THR B   4    8.838  17.421  20.262  O

ATOM     16  CG2  THR B   4    9.750  19.555  19.976  C
```

Residue number	1 2	2 7	3 6	Connectivity Matrix with Rc = 7^0A		
1	0	**3.799379**	7.240477	0	**1**	0
2	**3.799379**	0	**3.820605**	**1**	0	**1**
3	7.240477	**3.820605**	0	0	**1**	0
4	10.106471	**6.74347**	**3.796397**	0	**1**	**1**
5	13.614868	10.42275	7.151896	0	0	0
5	14.591231	11.844375	8.350204	0	0	0
6	11.544847	9.098421	**5.770436**	0	0	**1**
7	11.877039	8.628344	**4.845438**	0	0	**1**
8	15.647388	12.491948	8.706012	0	0	0
9	15.473453	12.987713	9.527085	0	0	0
10	13.504339	11.073862	8.058055	0	0	0
.	…………………………………………………………					
40	14.023911	10.772484	10.281037	0	0	0
41	12.516795	9.493806	9.396443	0	0	0
42	9.545317	**6.183155**	**5.71056**	0	**1**	**1**
43	9.088929	**5.483605**	**4.729272**	0	**1**	**1**
44	10.230778	7.480741	8.173551	0	0	0
45	8.657581	**6.523596**	8.371208	0	**1**	0
46	**6.545473**	**4.861921**	7.204947	**1**	**1**	0
47	9.402771	7.494949	8.481224	0	0	0

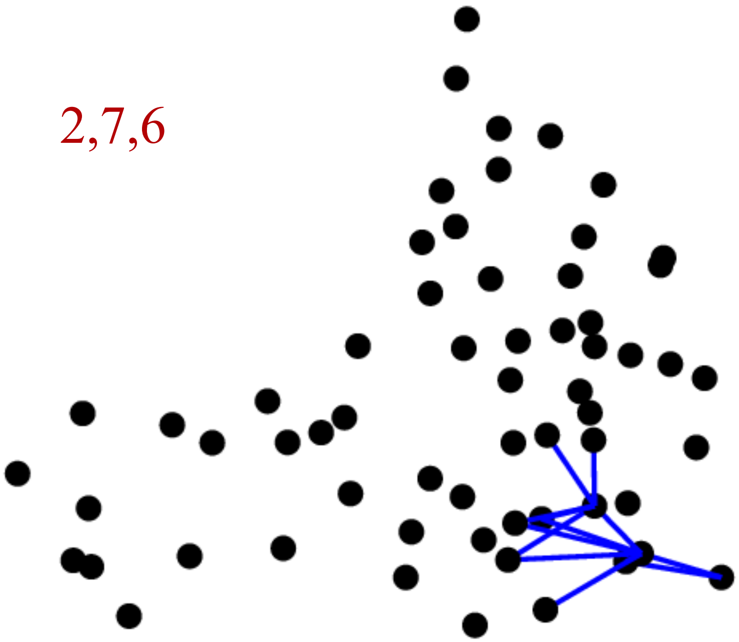
……………………………………………………………………

Euclidian Distance Matrix **Adjacency Matrix**

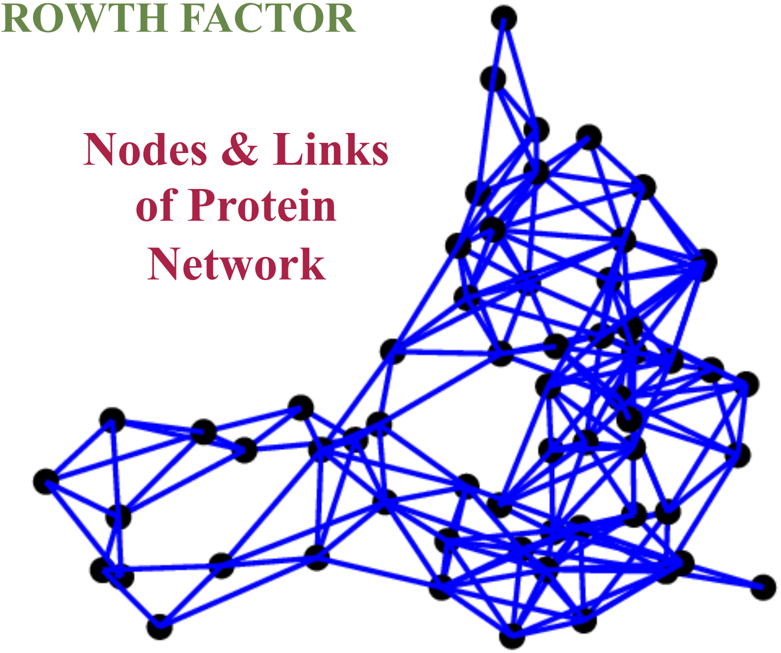
HUMAN INSULIN-LIKE GROWTH FACTOR



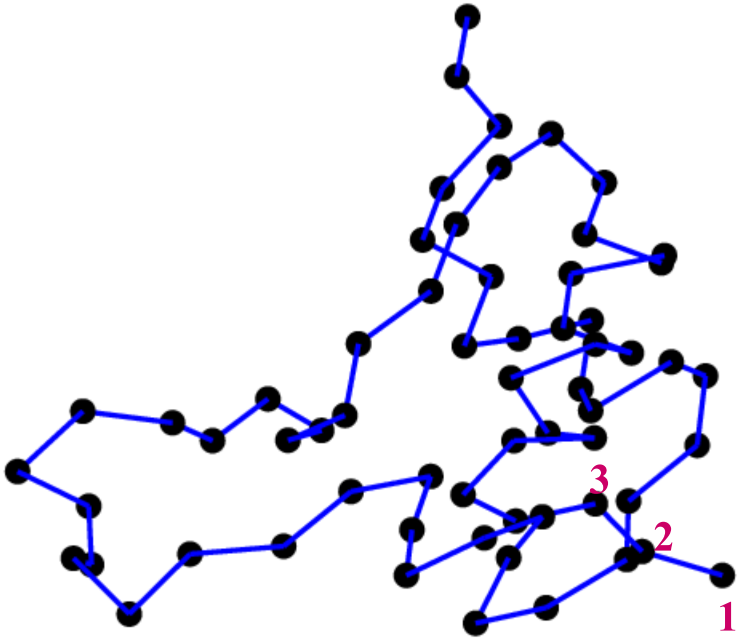
2,7,6



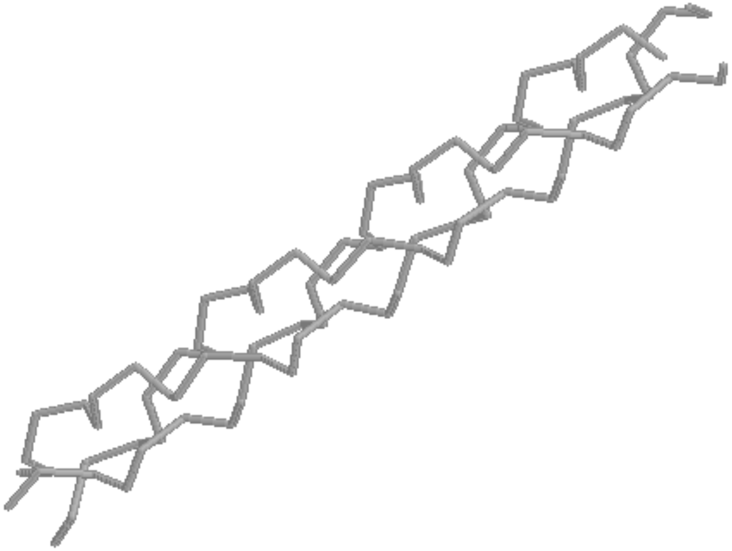
NETWORK CONSTRUCTION

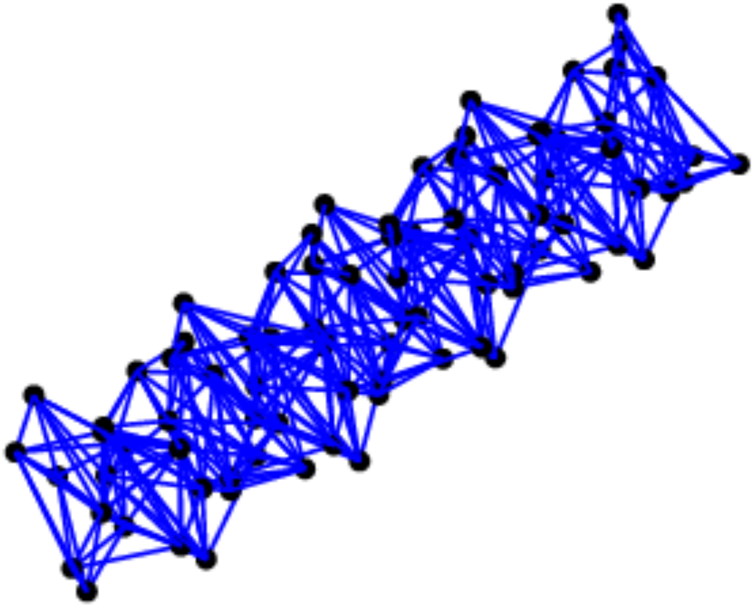


Nodes & Links of Protein Network

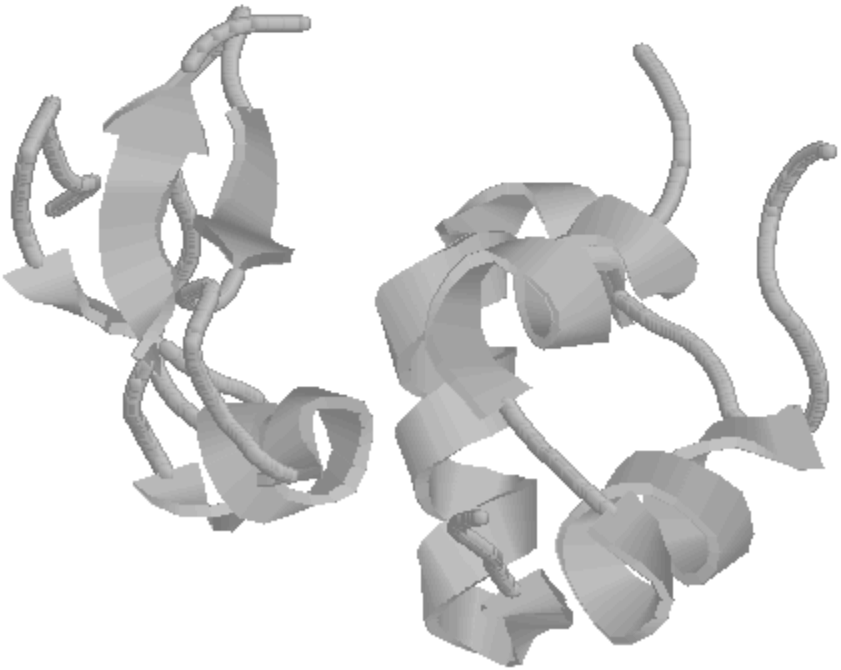


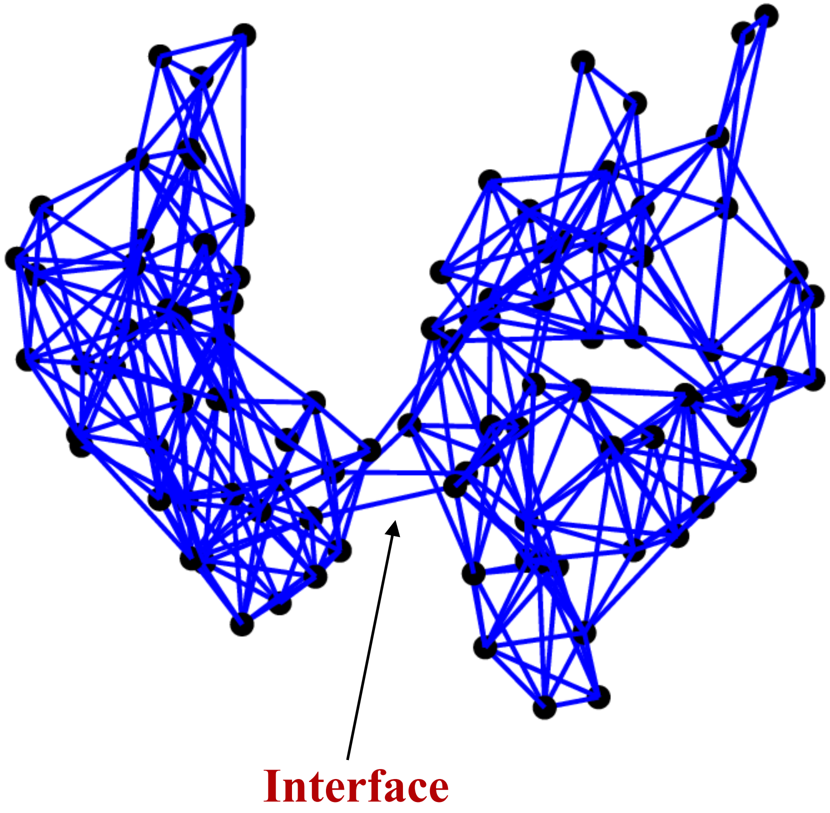
Fibrous Protein : Backbone picture and network model (1qsu)





A Protein : Cartoon and network model (1h59)





Long-range Interaction Networks in Protein Structures

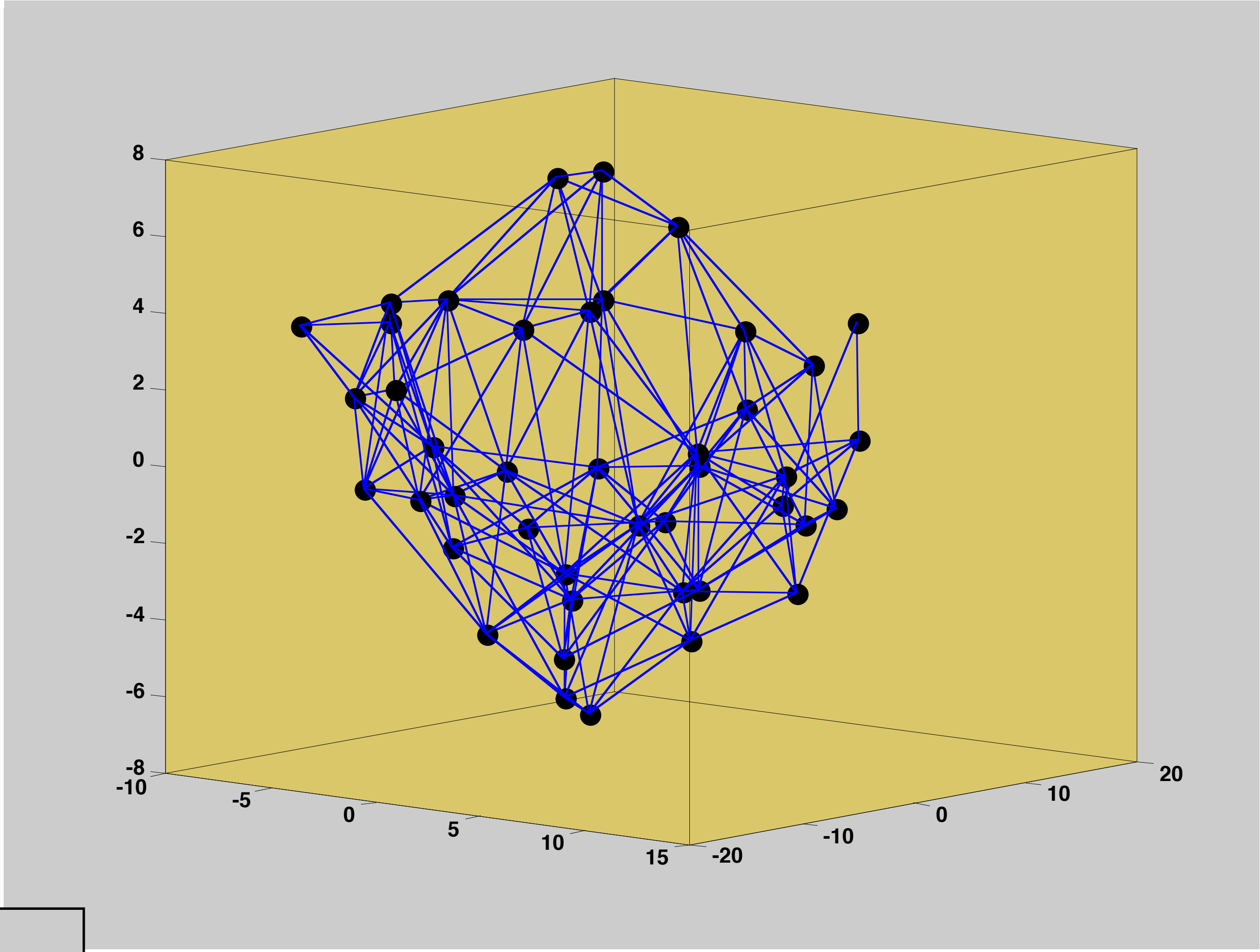
Long-range interactions are known to play a distinct role in determining the tertiary structure of the proteins, as opposed to the short-range interactions, which could be largely contributing to the secondary structure formations.

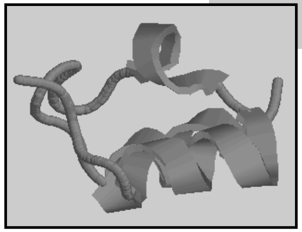
To study the contribution of the long-range interactions to topological properties, Long-range Interaction Networks (LRI/LIN) are obtained by considering only those spatial contacts which occur between nodes that are 'distant' (12 amino acids) from each other along the polypeptide chain.

(Typical lengths of an α helix and a β strand are 11 and 6 residues)

LRI is a subset of the amino acid network with same number of nodes but fewer number of links

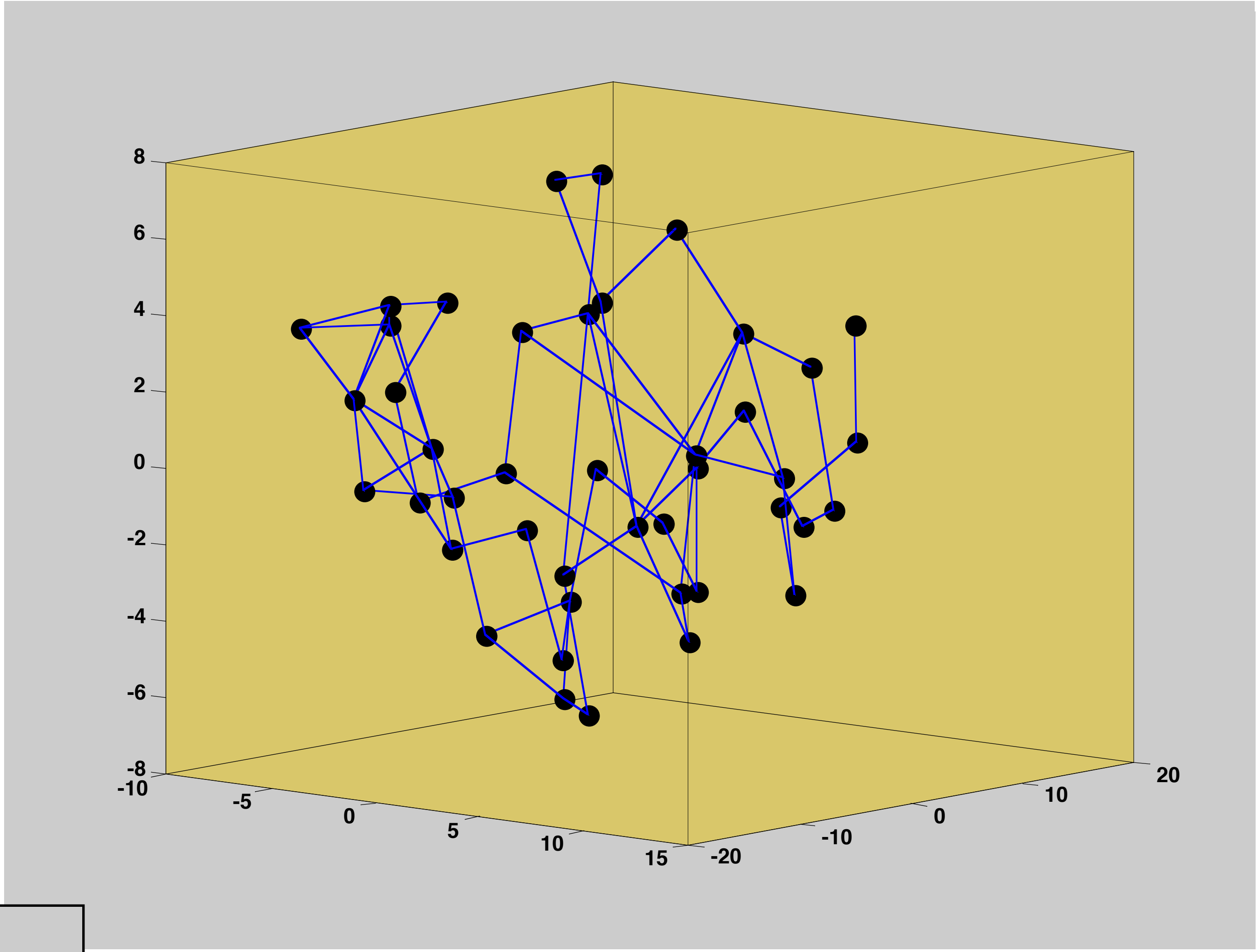
BUILDING PROTEIN NETWORK MODELS

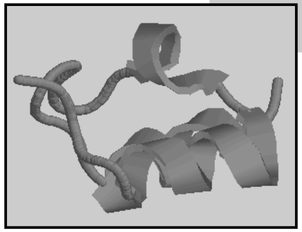




Protein Contact Network (PCN)

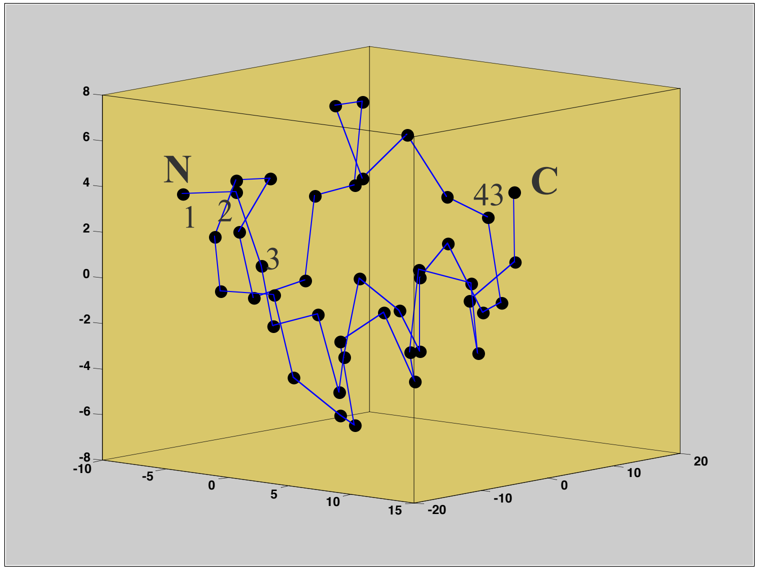
BUILDING PROTEIN NETWORK MODELS

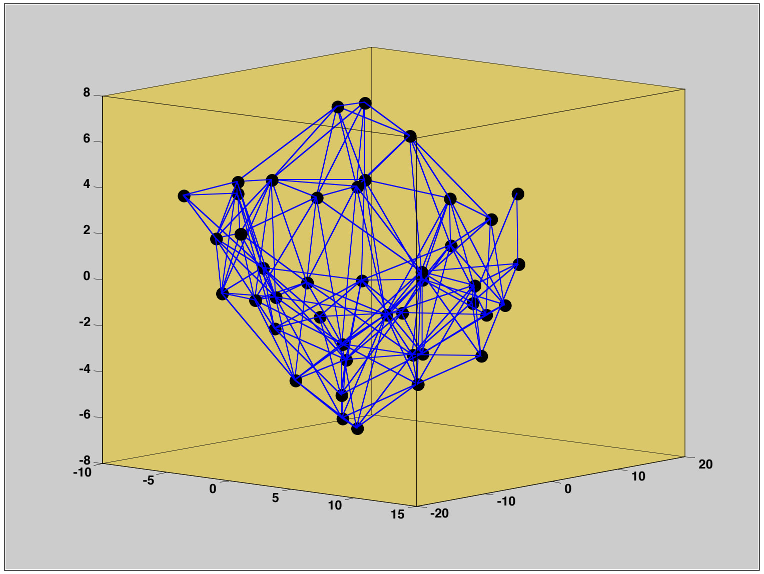


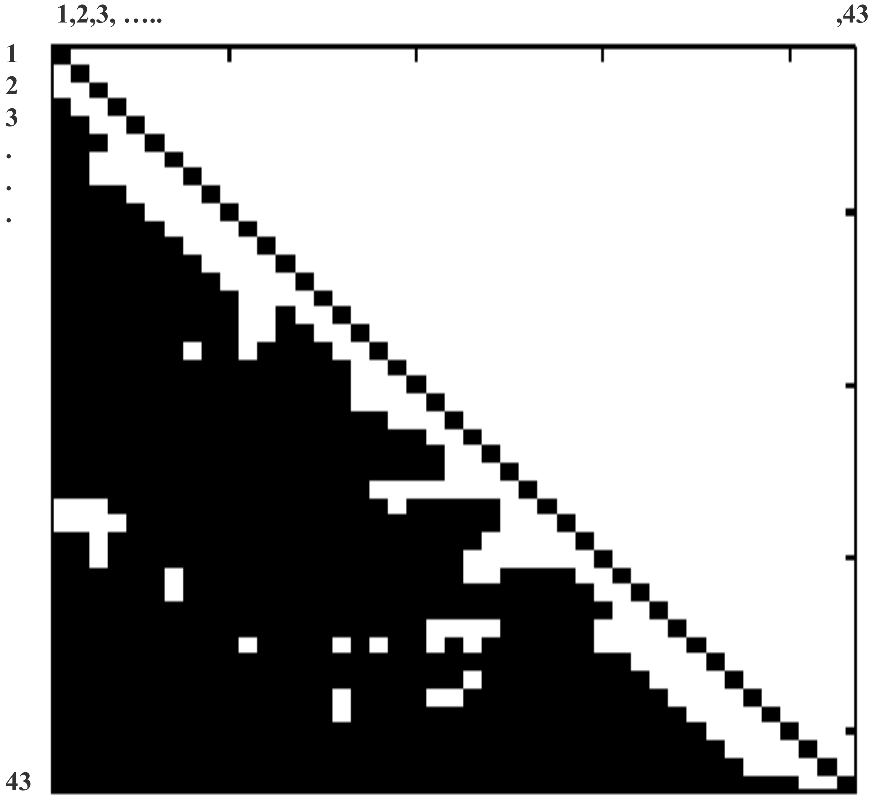


Long-range Interaction Network (LIN)

CONTACT MAP— A 2-D PICTURE OF PROTEIN

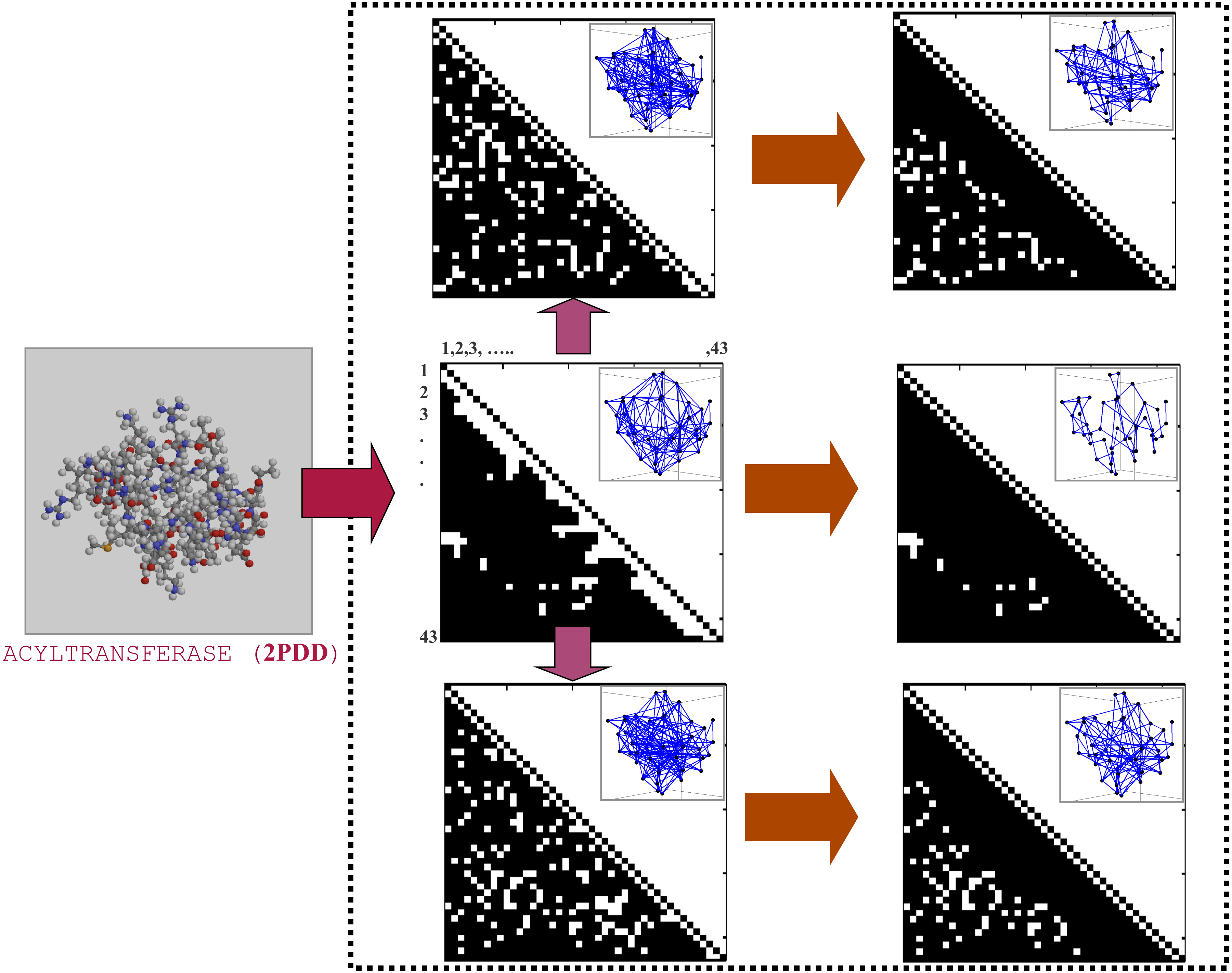






■ Residues *not* in contact.

□ Residues make a contact.


ACYLTRANSFERASE (2PDD)
1,2,3, …..
,43
1
2
3
.
.
.
43

“Networks offer a new way to categorize systems of very different origin under a single framework.

This approach has uncovered unexpected similarities between the organization of various complex systems, indicating that the networks describing them are governed by generic organization principles and mechanisms.

Understanding the driving forces which invest different networks with similar topological features enables us to combine the numerous details about molecular interactions into a single framework, offering means to address the structure of the biological system as a whole.”